

Human Adaptation to High Altitude: Regional and Life-Cycle Perspectives

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ABSTRACT Studies of the ways in which persons respond to the adaptive challenges of life at high altitude have occupied an important place in anthropology. There are three major regions of the world where high-altitude studies have recently been performed: the Himalayas of Asia, the Andes of South America, and the Rocky Mountains of North America. Of these, the Himalayan region is larger, more geographically remote, and likely to have been occupied by humans for a longer period of time and to have been subject to less admixture or constriction of its gene pool. Recent studies of the physiological responses to hypoxia across the life cycle in these groups reveal several differences in adaptive success. Compared with acclimatized newcomers, lifelong residents of the Andes and/or Himalayas have less intrauterine growth retardation, better neonatal oxygenation, and more complete neonatal cardiopulmonary transition, enlarged lung volumes, decreased alveolar-arterial oxygen diffusion gradients, and higher maximal exercise capacity. In addition, Tibetans demonstrate a more sustained increase in cerebral blood flow during exercise, lower hemoglobin concentration, and less susceptibility to chronic mountain sickness (CMS) than acclimatized newcomers. Compared to Andean or Rocky Mountain high-altitude residents, Tibetans demonstrate less intrauterine growth retardation, greater reliance on redistribution of blood flow than elevated arterial oxygen content to increase uteroplacental oxygen delivery during pregnancy, higher levels of resting ventilation and hypoxic ventilatory responsiveness, less hypoxic pulmonary vasoconstriction, lower hemoglobin concentration, and less susceptibility to CMS. Several of the distinctions demonstrated by Tibetans parallel the differences between natives and newcomers, suggesting that the degree of protection or adaptive benefit relative to newcomers is enhanced for the Tibetans. We thus conclude that Tibetans have several physiological distinctions that confer adaptive benefit consistent with their probable greater generational length of high-altitude residence. Future progress is anticipated in achieving a more integrated view of high-altitude adaptation, incorporating a sophisticated understanding of the ways in which levels of biological organization are articulated and a recognition of the specific genetic variants contributing to differences among high-altitude groups. *Yrbk Phys Anthropol* 41:25-64, 1998. © 1998 Wiley-Liss, Inc.

TABLE OF CONTENTS

Glossary	26
History of Human High-Altitude Habitation	29
Duration of high-altitude occupation by region	29
The Himalayan (Tibetan) plateau	29
Consideration of cultural influences	31
High-Altitude Adaptation Across the Life Cycle	33
Pregnancy and fetal life	33
Fetal wastage/pregnancy loss	34
Intrauterine growth and pregnancy duration	34
Maternal oxygen transport responses to pregnancy	36
Neonatal, infant, and maternal mortality	39
Infant, childhood, and adolescent development	41
Oxygen-transport characteristics	41
Growth and nutrition	44
Exercise performance	46
Illnesses	46
Adulthood and old age	47
Exercise performance	48
Characteristics of oxygen transport	49
Chronic mountain sickness (CMS) and other illnesses	54
Summary and Conclusions	55
Literature Cited	58

GLOSSARY

Alveolar-arterial oxygen difference [(A-a)DO₂]: The difference in oxygen pressure between the alveoli (A) and the arterial blood (a). This can vary as the result of changes in either of these variables, matching of pulmonary blood flow to the ventilated regions of the lung, membrane surface area, and/or diffusing capacity.

Arterial-mixed venous oxygen content (C_aO₂ - C_vO₂): The difference in oxygen content between the arterial blood and a mixture of all the venous blood returning to the heart from the different portions of the systemic circulation.

Arterial oxygen content (C_aO₂): The amount of oxygen in the blood, measured in milliliters/100 ml whole blood. It is best determined directly but can be calculated as ([hemoglobin] * 1.36 since each gram of hemoglobin theoretically binds 1.36 ml of oxygen.

Arterial oxygen saturation (S_aO₂): The percent of the heme groups in the hemoglobin molecule in the blood which are bound with oxygen.

Cardiac output: The volume of blood pumped by the heart per minute. It is the product of heart rate (beats/minute) and stroke volume (milliliters/beat). Stroke volume, in turn, is regulated by preload (right and left heart filling pressures), myocardial contractility (the percent of the ventricular volume expelled/beat), and after load (pulmonary and systemic blood pressure or vascular resistance).

Exercise capacity (VO₂max): The maximal work performance or amount of O₂ that can be consumed by the tissues. It is conventionally measured as the level of O₂ consumption at which an increase in work load of 25 watts or greater produces less than a 150 ml increase in O₂ consumption and is expressed as milliliters/minute/kilogram of body weight.

Exercise efficiency: The amount of work that can be performed at a given level of oxygen consumption.

Hemoglobin concentration: The amount of hemoglobin in the blood, usually expressed in grams/100 ml. It is comprised of hemoglobin able to bind or release oxygen (oxyhemoglobin, deoxyhemoglobin) as well as hemoglobin bound to other substances or unable to bind oxygen (carboxyhemoglobin, methemoglobin).

Hemoglobin-oxygen affinity: The extent to which oxygen is tightly bound to hemoglobin. This varies depending on the amount of oxygen present and the temperature, the pH, and the presence of other compounds in the blood. It is measured as the position of the hemoglobin-oxygen dissociation curve, often indexed as the P_{50} or the oxygen pressure at which hemoglobin is half-saturated with oxygen.

Heritability: The extent to which the expression of a trait is due to inherited as opposed to environmental characteristics in a particular environment.

Hypoxemia: Reduced oxygen delivery to the tissues as the result of lower blood oxygen content or reduced tissue blood flow.

Hypoxia: Reduced partial pressure of oxygen in the atmosphere at high altitude due to the lower barometric pressure.

Hypoxic ventilatory response (HVR): The magnitude of rise in ventilation over a 4–6 min period in which arterial O_2 tension or saturation is lowered from values typically present at sea level to those present at approximately 4,500 m (15,000 ft) while maintaining the levels of carbon dioxide in the expired air at the levels present under conditions of resting ventilation.

Lung volume: Total lung volume is comprised of the vital capacity (the maximal volume of air that can be forcibly expired out of the lung after a maximal inspiration) and the residual volume (the volume of air remaining in the lung after a forced expiration).

Pulmonary artery pressure (P_{PA}): The pressure in the blood flowing through the pulmonary arteries after being pumped by the right side of the heart to the pulmonary circulation. It is typically much lower than the pressure in the arteries being perfused by the left side of the heart, termed systemic blood pressure or simply blood pressure.

Sleep-disordered breathing: A fall or cessation in breathing during sleep, comprising apneas (cessation of breathing) and hypopneas (reduction in breathing), with a resultant decrease in S_aO_2 .

Ventilation: The amount of air breathed out per minute under resting conditions. It is also called minute or resting ventilation and is expressed in liters BTPS/minute. It includes air moving through the alveoli (areas of gas exchange) and dead space (bronchi, trachea), referred to as alveolar ventilation and dead space ventilation.

Nearly 140 million people reside at high altitude, defined here as elevations above 2500 m (8,000 ft) (Table 1). Studies of the ways in which these persons respond to the adaptive challenges of life at high altitude have occupied an important place in anthropology. Because the fundamental adaptive challenge of hypoxia (see Glossary) cannot be easily modified by culture, human biological responses can be clearly discerned. Cultural influences are not, however, absent, as they both condition biological responses and modify other attributes of the high-altitude environment, such as cold, aridity, and limited energy production. Thus, the fundamental contribution of high-altitude studies to anthropology has been to demonstrate the ways in which humans respond biologically to environmental stress and how biological responses, alone and together with cultural

factors, affect the process of adaptation. In this fashion, high-altitude studies serve as a useful complement to other areas of anthropology concerned with the products and processes of evolution.

Here and throughout, we use *adaptation* to refer to a feature of structure, function, or behavior that enables an organism to live and reproduce in a given environment (Dobzhansky, 1968). These features may be biological or behavioral in nature, genetic or developmental in origin. In most instances, a combination of factors is involved. By *genetic adaptation*, we mean a heritable characteristic whose presence reflects the operation of natural selection or other evolutionary forces (genetic drift, gene flow, mutation) over time. We use *developmental responses* to refer to those occurring after prolonged exposure to stress(ors) during the period of growth and development. While

TABLE 1. Estimated numbers of persons residing >2,500 m in 1995 Hammond, 1934;
(World Health Organization, 1996)

Region, country, province or state	Total population	Annual population growth (%)	Estimated ¹ % >2,500 m	Estimated number >2,500 m
Africa				24,301,950
Ethiopia	55,053,000	2.9	25	13,763,250
Kenya	28,261,000	2.1	10	2,826,100
Rwanda	7,952,000	2.6	15	1,192,800
Uganda	21,297,000	2.9	10	2,129,700
Zaire	43,901,000	2.1	10	4,390,100
Asia				78,677,965
Afghanistan	20,141,000	5.6	10	2,014,100
Bhutan	1,638,000	2.4	45	737,100
China	1,221,462,000	1.0	~2	22,094,700
Inner Mongolia	8,960,000		20	1,792,000
Qinghai	4,120,000		40	1,648,000
Sichuan	104,070,000		5	5,203,500
Tibet	2,150,000		80	1,720,000
Yunnan	31,920,000		20	6,384,000
Xinjian Uygur				
Zizhiqu	13,368,000		40	5,347,200
India	935,744,000	1.8	~3	26,815,115
Himchal Pradesh	4,269,569		30	1,280,871
Jammu and Kashmir	6,981,600		40	2,792,640
Sikkim	425,000		40	170,000
Utar Pradesh	112,858,019		20	22,571,604
Kazakstan	14,984,100	2.3	20	2,996,820
Kirghizistan	4,698,000	2.5	10	469,800
Nepal	21,918,000	2.5	35	7,671,300
Pakistan	140,497,000	2.8	10	14,049,000
Tajikistan	6,101,000	2.7	30	1,830,030
Central and South America				35,821,750
Argentina	34,587,000	1.2	5	1,729,350
Bolivia	7,414,000	2.3	40	2,965,600
Chile	14,262,000	1.4	10	1,426,200
Colombia	35,101,000	1.5	20	7,020,200
Ecuador	11,460,000	2.0	15	1,719,000
Guatemala	10,621,000	2.8	10	1,062,100
Mexico	93,674,000	1.8	15	14,051,100
Peru	23,780,000	1.8	20	4,756,000
Venezuela	21,844,000	2.0	5	1,092,200
North America				383,900
US	263,250,000	0.9	<1	383,900
Colorado	3,068,000		10	306,800
Utah	1,542,000		5	77,100
Total				139,185,565

¹ Population estimates >2,500 m for each country, province, or state were made using the total population size, geographic area >2,500 m, population size of the largest cities, and population density.

developmental processes are sometimes considered distinct from genetic ones, it is important to recognize that the capacity to acquire the trait may be genetically based. *Acclimatization* is used to refer to the time-dependent physiological responses that occur following exposure to high altitude. The distinction between these terms is that adaptations confer evolutionary benefit (enhanced fitness), whereas physiological responses simply occur and may or may not be adaptive.

Previous reviews have provided excellent coverage of human adaptation to high altitude (Moore and Regensteiner, 1983; Baker et al., 1978; Baker and Little, 1976; Winslow and Monge, 1987). One major question addressed by these (and ongoing) studies is the extent to which the responses to high altitude are due to phenotypic plasticity in the adult vs. developmental or genetic processes (Frisancho et al., 1995, 1997; Greksa et al., 1985; Baker and Little, 1976). This review extends the time frame over which adapta-

tion is being viewed to include multiple generations. The central question here is whether the functional consequences of residence at high altitude vary in relation to the duration (in generations) of high-altitude residence and, if so, what physiological mechanisms are involved. The opportunity to ask this question has been provided by several in-depth studies conducted throughout the human life cycle in the Himalayan region of the world, an area which until recently was not readily accessible to outside observers, as well as numerous recent studies in the Andean and Rocky Mountain high-altitude regions. Our consideration excludes the East African highlands simply because of the lack of recent study in this region.

The organizational plan followed is first to review the geographical and historical circumstances of the Himalayan, Andean, and Rocky Mountain high-altitude residents to decide whether some groups have lived at altitude longer than others. We then survey the physiological responses to hypoxia described for each of these regions at each phase of the life cycle, namely pregnancy and fetal development, infancy, childhood, adolescence, adulthood, and old age. Of special interest are differences among these regions in the effects of altitude on a range of functionally significant traits, including fetal growth, subacute infantile and chronic mountain sickness, exercise performance, and whether such differences relate to duration (in generations) of high-altitude residence. Determining the physiologically relevant and, within the limits of current knowledge, genetically regulated processes of oxygen transport underlying these traits permits us to assign adaptive value to physiologic responses. We end with a consideration of the possible future directions for research on high-altitude adaptation. In particular, we address developments in evolutionary theory and genetic methodology that bear on our ability to detect and interpret genetic differences between populations. Incorporating such perspectives into future studies of high-altitude populations will advance our understanding of the specific ways in which genetic traits interact with physiological and cultural processes.

HISTORY OF HUMAN HIGH-ALTITUDE HABITATION

Duration of high-altitude occupation by region

The comparison of world high-altitude populations is of interest from an evolutionary perspective since populations which have spent the longest time at high altitude and which have the least degree of admixture from lowland populations can be expected to have genetically adapted. Other factors affecting the population's genetic composition also need to be taken into account, as these influence the genes available on which natural selection can act.

The Himalayan (Tibetan) plateau. The Himalayan (Tibetan) plateau is the largest and most geographically isolated of the high-altitude regions. It is roughly oval in shape, stretching 2,400 km (1,500 mi) east to west and 1,100 km (700 mi) along its north-south axis and encompassing over 200 million hectares (over 800,000 square miles). The distance to the nearest sea coast, the Bay of Bengal, ranges from 800–2,400 km (500–1,500 miles). On the south, it is flanked by the world's highest mountains and by peaks reaching 7,600 m on the north, west, and east. Only at the northeastern edge does it descend gradually to the low-altitude region drained by the Huang (Yellow) River.

Hominids have been present in Asia for a million or more years, longer than the duration of hominid occupation of North and South America. Paleoliths and microliths consistent with northern Asian tool cultures of the Upper Paleolithic, dating to approximately 25,000–50,000 years ago, have been found at 4,500–5,200 m on the northern Tibetan plateau (Sensui, 1981; Beck and D'Amore, 1997). Even older material from the late Pliocene (approximately 2 million years ago) has been reported immediately adjacent to the Tibetan plateau in northern Pakistan (Denell et al., 1988). Material dated in situ is more recent, consisting of farming implements that are 5,000 years old (Chang, 1992). While these data cannot provide assurance of genetic continuity or indicate when permanent occupation of the plateau began, they support the possibility that hu-

mans have been on the Tibetan plateau for upwards of 50,000 years.

Genetic and linguistic studies also support a long period of residence for the Tibetan population in its current location. Dental morphology and mitochondrial and nuclear genetic markers show Tibetans to be related to Korean, Siberian, and Mongolian populations and to differ considerably from Han ("Chinese") and other southeast Asian populations (Matsumoto, 1987; Torroni et al., 1994b; Turner, 1987; Lee et al., 1988; Zhao and Lee, 1989). The Tibetans' membership in the Tibeto-Burmese language group differentiates them from southeast and north-central Asian (including Mongolian) populations and indicates that Tibetans have resided in their south central location long enough for linguistic separation to have occurred. Contact has occurred between Tibetans and other populations via trade and, in the thirteenth and fourteenth centuries, conquest by Mongolians. But the major trading routes (e.g., the Silk Road) avoided the Tibetan plateau, and the period of Mongolian domination was relatively brief (~100 years) and more in the form of patronage than subjugation (Avedon, 1986). Therefore, occupation of Tibet by foreigners has been relatively limited until recently in terms of geographic penetration and impact on survival and well-being. Genetic divergence increases when populations are separated by physical, linguistic, and other cultural barriers such as characterize the western, southern, and eastern boundaries of Tibet (Farabegoli and Barbujani, 1990; Zei et al., 1993). Thus, the expectation would be that Tibetans are genetically distinct from adjacent populations except those to the north. However, no specific genetic admixture estimates are available between Tibetans and adjacent populations, including Sherpas and Mongolians. Such information is needed to determine admixture rates and a more specific genetic history for this region of the world.

The Andean altiplano extends nearly 4,800 km (3,000 miles) along nearly the whole of South America, averaging 200 km (125 miles) wide and encompassing nearly 100 million hectares (400,000 square miles). The Amazon River basin extends to the east, and

broad grassland plains flank its southernmost portion. The Pacific coastline parallels the altiplano 75–150 km (50–100 mi) to the west. The region between the altiplano and Pacific coast is generally dry but is punctuated by littoral plains, irrigated valleys, and broad harbors.

Andean residents are likely to be descendants of north-central Asian populations who migrated in several waves over the Beringian land bridge which was exposed periodically between 65,000 and 15,000 years ago (Neel et al., 1994). There is comparatively little mitochondrial DNA (mtDNA) variation among the indigenous populations of the Americas; existing variation can be accounted for by as few as four mtDNA lineages (Merriwether et al., 1995; Chen et al., 1995; Torroni et al., 1993). This may reflect the operation of a founder effect resulting from a small number of migrants (e.g., as few as four women plus some men) or to limited mtDNA variation among a larger number of persons. Archaeological evidence suggests that humans were present in South America as early as 9,000–12,000 years ago (MacNeish and Berger, 1970; Lynch, 1978; Nunez, 1983). Again, these archaeological data do not provide assurance of genetic continuity between ancient and current inhabitants of the Andes. Domestication of the potato, quinoa and other grains, camelids (llamas, alpacas), and guinea pigs began about 6,000 years ago and was complete by 4,000 years ago (MacNeish and Berger, 1970; Lynch, 1978; Nunez, 1983). Surprisingly, Quechua and Aymara belong to separate mtDNA lineages (Merriwether et al., 1995) and linguistic groups, even though they reside next to each other on the altiplano and have much in common with each other culturally. Such patterns of mtDNA variation may indicate considerable stability and separation of maternal lineages or be the result of stochastic, genetic drift within small populations (Blanco and Chakraborty, 1975).

The Pacific coast was the point of contact between the Andean civilizations and the European powers in the 1500s. Contact had devastating consequences; not only were Andean rulers killed and cities looted but, within 100 years following conquest, population size declined from 12 million to 675,000

due to pandemics of infectious disease, malnutrition, and forced resettlement (Cook, 1981). The loss of 95% of the precontact indigenous population meant that the surviving fraction underwent an evolutionary bottleneck. Together with the limited genetic variation stemming from a founder effect, such an evolutionary bottleneck has likely diminished the amount of genetic variation in current Andean inhabitants. It is also unclear whether the fraction surviving (~5%) represented that portion of the population that had resided at high altitude. There has been some subsequent admixture with European-derived populations. Current estimates in Ecuador, Peru, and Bolivia vary from 5–30% (Blanco and Chakraborty, 1975; Chakraborty et al., 1989; Post et al., 1968; R.E. Ferrell, personal communication) and show a good correlation with surname (Chakraborty et al., 1989). In persons with Aymara patronyms and matronyms, 89% of the genes surveyed were of Amerindian origin, whereas Spanish-surnamed individuals had less (67%) although nonetheless substantial Indian ancestry.

The Rocky Mountain plateau encompasses an oval region, approximately 1,200 km (750 miles) long and 400 km (250 miles) wide or nearly 40 million hectares (150,000 square miles) in Wyoming, Colorado, Utah, and New Mexico of the western United States, with the highest segment being in Colorado. Amerindians lived seasonally in this region, but it was not inhabited permanently until 150 years ago. Its current residents are genetically heterogeneous, having descended from low-altitude Amerindian, European, and Hispanic populations. Thus, the high-altitude populations of the Rocky Mountain region are, by virtue of their short period of residence, not genetically adapted to high altitude.

In summary, it is likely that persons have lived the longest on the Tibetan plateau, for an intermediate length of time on the Andean altiplano, and for the shortest length of time in the Rocky Mountain region. The greater size, geographic isolation, remoteness from coastal regions, and absence, until recently, of conquest by low-altitude groups also suggests that the residents of the Tibetan Plateau have been subject to less

reduction in genetic variation and less genetic admixture with low-altitude groups than the Andean residents.

Consideration of cultural influences

High-altitude residents employ cultural practices that modify environmental stressors and thus condition biological responses. Indigenous cultural practices affecting food sources, energy expenditure, and population movement provide examples of the ways in which such conditioning takes place.

Plants and animals genetically adapted to high-altitude environments traditionally have been relied upon as food sources. In Tibet, barley is the staple, with green vegetables being added in the summer and dried vegetables and root crops such as potatoes and turnips eaten in the winter (Kolsteren et al., 1990). Andean staples consist of numerous tubers (over 2,500 kinds of kinds of potato, *ulloco*, *oca*, *mashua*), quinoa, and other grains (*kiwicha*, *tarwi*, *cannihua*) (Richardson, 1994). The Quechua practice of freeze-drying potatoes (*chuño*) and meats (*charqui*) preserves them for long periods and reduces their weight, facilitating transport by groups using widely dispersed resources (Thomas, 1976). Other crops (peanuts, beans, fruits, and coca) from low-altitude regions supplement the Andean diet and, in the case of coca, have nutritional as well as narcotic effects (Richardson, 1994). Animals indigenous to the high-altitude environment—the llama and guinea pig of the Andes and the yak of the Himalayas—are efficient producers of food, clothing, and fuel. The llama and yak particularly have multiple uses, being a source of transport, meat, wool, rope, leather, dung for fuel and fertilizer, and, in the case of the yak, milk for butter, cheese, and yogurt as well as labor for pulling the plow.

Exchange of resources between altitudes plays an important part in high-altitude regions. In the Andes, an extensive network of Inca roads or wide footpaths links the highland and lowland areas. This network has been joined more recently by highways, railroads, and air travel. Animal resources (wool, hides, meat) from the Andean altiplano are exchanged for wheat and other foods grown at lower elevations (Thomas,

1976). In Tibet, most exchange of crops and animal products occurs between farmers and pastoralists within a region (Kolsteren et al., 1990). Between regions, trade routes and relationships between monasteries served historically to move products over longer distances. Until the 1950s, nearly all trade was by foot or pack animal, as wheeled vehicles were prohibited by Buddhist beliefs and railroads have yet to penetrate the Tibetan plateau. Recently, highways and air travel have linked the Tibetan plateau with lowland regions.

Concentrated deposits of minerals with high monetary value are exposed in the mountainous environment and contribute importantly to economic exchanges in the Andean and Rocky Mountain regions. Mining has also been practiced on the Tibetan plateau but to a lesser extent. The monetary value justifies high levels of expenditure for employing large numbers of persons and purchasing, in the case of Rocky Mountain residents, virtually all the required foodstuffs from low-altitude regions. Recreational tourism provides an increasingly important source of income for Rocky Mountain residents.

Exchanges within households are important in the production and consumption of resources. In traditional subsistence economies, food is generally produced by adults and adolescents and distributed to the young and older-aged members of the household. This pattern serves to minimize seasonal change in caloric consumption. For example, in rural highland Peru, preharvest household caloric consumption was less than half that present postharvest (Leonard and Thomas, 1989). However, preferential distribution of food to children, the reduction of household consumption by changes to less energy-intensive activities, and the temporary out-migration of adolescent and adult males protected children from seasonal shortages (Leonard, 1991). The use of children or adolescents in herding serves to reduce household caloric consumption, since a 12-year-old child can complete the herding work of an adult with 30% fewer calories (Thomas, 1976). In the Lhasa valley, men and women eat the same kinds and generally the same amounts of food. The relation-

ship of food need to energy expenditure is recognized by Tibetan farmers; those who do the most work eat the most regardless of sex (Kolsteren et al., 1990).

Conservation of energy is accomplished by the use of housing and clothing with properties that minimize heat loss and maximize heat gain. Houses made of adobe, thick mortared stone, or sod bricks on the Andean and the Himalayan plateaus have insulating value and effectively store radiant heat gained during the almost universally sunny days. Houses of piled stone construction provide little buffering against cold but represent a lesser energy and resource investment for mobile pastoralist families in both locations. Clothing creates a warm, portable living environment, typically consisting of multiple layers of insulating fiber (usually wool). The outer layer is often dark, tightly woven, and water-resistant and serves to maximize solar heat absorption and prevent convective heat loss. Covering for the head and face provides shielding and helps maintain a warmed, humidified microenvironment around the face. The limited availability of wood or other fuel for heating houses makes the strategy of fully clothed family members sleeping together an important means of conserving body temperature without increased expenditure of caloric energy or fuel resources (Hanna, 1976).

Specific cultural practices afford additional protection from environmental stresses around periods of vulnerability in the life cycle. For example, in both Peru and Tibet, the infant or young child sleeps with the mother in the early months of life, is nursed in the warmest location, remains swaddled even while indoors, and is placed in the sunniest areas when outside. The infant is wrapped in multiple layers—diapering, leggings, an inner garment, and sweater—and wears a knitted hat (Baker, 1976; Niermeyer, unpublished observations). In Tibet, infants are carried inside the traditional outer garment (chuba) so nursing can occur within protective layers of clothing. Quechua and Aymara women in the Andes carry their infants using a carrying cloth or manta worn across the mother's back and fully enclosing the infant, who is also encased in a blanket and swaddled by a cloth

belt. The insulating value of this manta pouch is sufficient to raise relative humidity and temperature 12°C from the first layer of the pouch to the infant's skin but inspired PO_2 is 8–16 mmHg below ambient (Tronick et al., 1994). The adoption of Western-style dress by mothers in the Lhasa valley appears associated with a higher incidence of cold injury in their infants, suggesting that the abandonment of long-standing clothing and carrying practices is maladaptive (Niermeyer, unpublished observations).

Another example of a cultural practice which affords protection from the high-altitude environment is permanent or temporary out-migration, perhaps the ultimate behavioral solution to an environmental problem. Such practices were recorded in the Andes by the seventeenth-century historian Antonio de la Calancha, who observed that pregnant women of Spanish origin descended to give birth at lower altitudes and did not return until the child was more than a year old (Monge, 1948). A similar practice occurs today among pregnant Han women in Tibet, who typically descend to their home districts at or near sea level and remain there or leave their infants with extended family until the infant is approximately 2 years of age (Niermeyer et al., 1995). Colorado high-altitude residents also illustrate this pattern, moving to lower altitudes after age 55 in order to alleviate symptoms of heart and/or lung disease (Regensteiner and Moore, 1985).

In summary, high-altitude residents engage in cultural practices that lessen the effects of hypoxia for limiting energy availability in the high-altitude environment. Historical as well as present-day Himalayan and Andean residents rely on well-adapted indigenous plants and animals to produce calorically dense food. By seasonal adjustment in energy expenditure and food consumption within households, resources are distributed in ways that protect infants and children at times of shortage. House construction and clothing aid in the conservation of energy. In the Andes and Rocky Mountains, trade between regions, highly valued mineral resources, and, particularly in North America, recreational opportunities augment the resources available. Close

proximity to different climatic zones provided by the vertical layering of the highland environment facilitates such resource exchange.

HIGH-ALTITUDE ADAPTATION ACROSS THE LIFE CYCLE

The stages of the human life cycle provide a convenient framework for reviewing the physiological responses to hypoxia and demonstrating how these responses influence the ability of one generation to successfully reproduce the next (adaptation). Life-cycle analysis has had broad and productive application within biological anthropology (Smith and Tompkins, 1995). In this section, we consider pregnancy and fetal life, infancy, childhood, and adolescence, and adulthood and old age. Mortality risk is unequally distributed across these phases; it is greatest during fetal life, intermediate during infancy and childhood, and lowest in adolescents and adults (except for women during child-bearing years) until the oldest ages. The early period is of the greatest interest from an evolutionary point of view since, in addition to increased mortality risk, reproduction has not been completed. There are also a greater number of studies which address the effects of high altitude during the earlier than the later phases of the life cycle. At each phase, we compare the effects of high altitude in the various regional populations and in high-altitude vs. sea-level residents or acclimatized newcomers, depending on the data available. The underlying question is the extent to which lifelong high-altitude residents of the Himalayan, Andean, and Rocky Mountain regions differ in their physiologic responses to hypoxia and whether such differences support the likelihood that some populations have adapted to high altitude.

Pregnancy and fetal life

From an evolutionary perspective, pregnancy represents a critical overlap between the generations. While the health risk to the fetus and neonate is greater than that of the mother, the evolutionary effect of a maternal death is magnified since it results in the loss of two individuals, mother and fetus, and

curtails the father's genetic contribution as well.

Fetal wastage/pregnancy loss. Fetal wastage/pregnancy loss is usually assessed by careful monitoring of completed fertility (total number of births per women aged 15–44 years), spontaneous abortions, or miscarriages. In practice, such information is difficult to obtain. Fertility has been reported to be reduced in the Andean region compared to sea level as judged by smaller completed family size, a shortening of the reproductive span by later menarche and earlier menopause, and an increase in completed fertility in persons who migrated from high to low altitudes (Abelson, 1976). Other studies in South America and Nepal do not support an altitude-associated reduction in fertility and in fact suggest higher completed fertility at high than low altitudes (Gonzales, 1993; Goldstein et al., 1983; Cruz-Coke et al., 1996). Higher fertility is achieved in highland Peru and Chile by shorter intervals between births and an increased frequency of conception during lactation. Births are likely underenumerated in the Andean and Himalayan regions, where less than half the women deliver in hospitals (Pan American Health Organization, 1994). High neonatal (birth to 28 day) or infant (birth to 1 year) mortality likely increases fertility by prompting a greater number of births to assure surviving offspring but may reduce reported fertility as the result of incomplete tallying of infants in periodic censuses. Cultural practices affecting exposure to intercourse (e.g., proportion of the population living as celibate nuns) as well as the contribution and costs of children also influence childbearing patterns. In rural highland Peru, children generate more resources than they consume, making high completed fertility desirable (Thomas, 1976).

Endocrinological studies suggest alterations in reproductive function at high altitude. Andean highland women had similar levels of luteinizing hormone but lower prolactin levels compared to low-altitude women (Gonzales and Guerra-Garcia, 1993). Urinary ovarian hormone levels were essentially the same, but serum progesterone was elevated and estrogens (estradiol and es-

triol) reduced during high- compared to low-altitude pregnancy in Colorado and Peru (Sobrevilla et al., 1971; Zamudio et al., 1994). Measures of testicular function were similar, but testosterone levels were lower at 4,340–4,500 m than at 150 m in Peru. Sherpa males at high compared with low altitude have lower serum luteinizing hormone and a trend for lower follicle stimulating hormone levels, suggesting less stimulation of the pituitary gland (Bangham and Hackett, 1973). Thus, there may be some level of impairment of reproductive function at high altitude, but it is not sufficient to limit or even reduce fertility.

Intrauterine growth and pregnancy duration. One of the best-documented effects of high altitude is a progressive reduction in birth weight. Birth weights decline an average of 100 g per 1,000 m altitude gain in studies conducted over a 40 year period (Fig. 1). In addition to the lower mean birth weight, the percentage of low-birth-weight babies (<2,500 g) is fourfold greater at high (>2,700 m) than low altitude in a US population-based study (Yip, 1987). The reduction in birth weight is due to direct effects of high altitude and not interactive effects with other risk factors such as maternal age, parity, body size, or prenatal care (Jensen and Moore, 1997). Similar birth-weight reductions under other circumstances of reduced fetal-placental oxygen supply implicate the hypoxia of high altitude as causative. The reduction in birth weight at high altitude has historical significance; the first recognition that fetal growth and length of gestation were separable influences on birth weight on a population level was made at high altitude (Lichty et al., 1957).

The primary cause of the reduction in birth weight is retardation of intrauterine growth rather than shortened gestation. Babies are both lighter and shorter for gestational age, conforming to a model of growth retardation throughout pregnancy, with the greatest absolute reduction in fetal size occurring in the mid to late third trimester (McCullough et al., 1977; Unger et al., 1988). Average gestational ages at high vs. low altitude are generally similar (Table 2), but accurate data are difficult to obtain, particu-

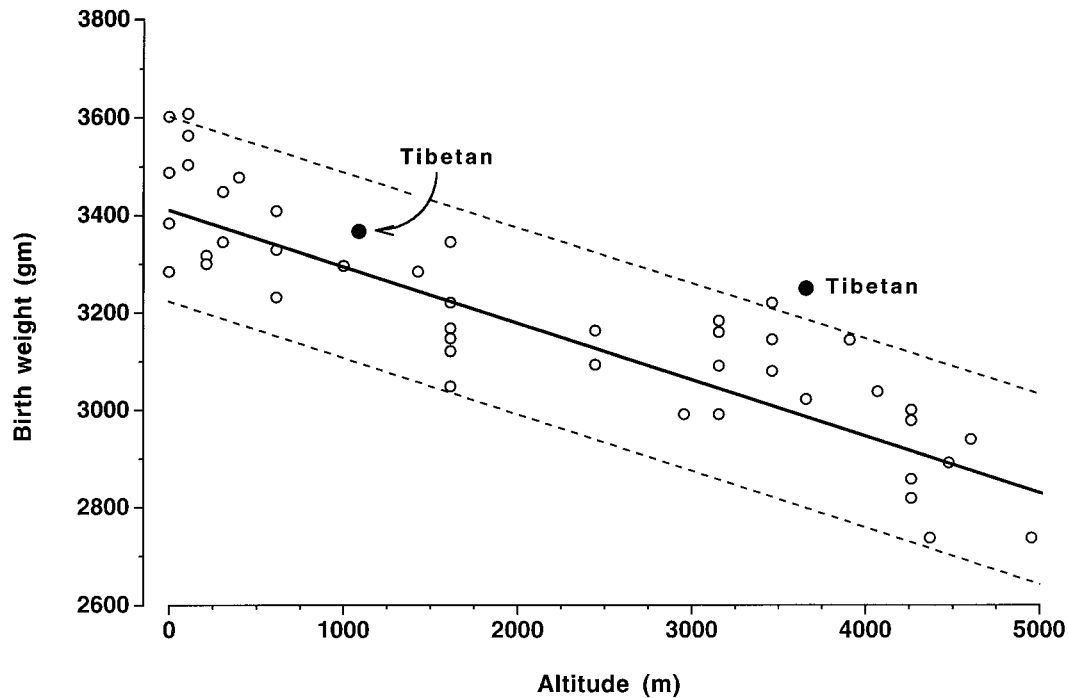


Fig. 1. Mean birth weights from previously published studies in groups of high-altitude residents of North America, South America, and Tibet (labeled) with the upper and lower 90% confidence limits (dotted lines). (Reproduced from Moore et al., 1994, with permission of the publisher).

larly in developing countries which lack universal, standardized reporting of birth weight and gestational age.

Existing data suggest that the magnitude of fetal growth retardation varies in relation to the duration of high-altitude residence, with the longest resident populations experiencing the least decline and the shortest resident groups demonstrating the most reduction in birth weight. This is supported in several ways. First, heavier birth weights are generally seen in Tibetans than Andean or Rocky Mountain residents of the same altitude (Fig. 1). The protection from altitude-associated reductions in birth weight has also been observed for Nepalese Sherpa (Smith, 1997) but not Ladakhis in northern India (Wiley, 1994). Only 6% of this Ladakh sample was Tibetans; the remainder was Indian or of other origin. Second, comparisons of birth weights collected by the same investigator from women of the same genetic background residing at sea level vs. 3,100–3,600 m reveal the greatest birth-

weight reduction in the Rocky Mountain region (-352 g, $P < 0.001$), an intermediate decline in Andeans (-270 g in Peru, -282 g in Bolivia, $P < 0.001$), and the least change in Tibetans (-72 g, $P = \text{NS}$) (Zamudio et al., 1993a). Third, at the same elevation (3,600 m), women of high-altitude ancestry give birth to heavier-birth-weight infants when compared with high-altitude residents who were born and raised at low altitude or with women born and raised at high altitude but descended from populations of low-altitude ancestry. In Tibet, babies born to lifelong residents of Tibetan ancestry weighed 294–650 g more than babies born to Han women who had lived there for several years (Niermeyer et al., 1995; Zhoma et al., 1989). In Bolivia, Aymara lifelong high-altitude residents gave birth to infants who weighed 143 g more than babies born to lifelong high-altitude residents of European or mestizo ancestry (Haas et al., 1980).

Thus, several factors appear involved in protecting long-term, native high-altitude

TABLE 2. *Effect of high altitude on birth weight, gestational age, and neonatal or infant mortality*

	Low altitude					High altitude				
	Altitude (m)	Weight (g)	Gesta- tional age (weeks)	Preterm %	Mortality rate	Altitude (m)	Weight (g)	Gesta- tional age (weeks)	Preterm %	Mortality rate
Rocky Mountains										
Lichty et al. (1957)	1,600	3,035			23.4 ²	3,100	2,655 ¹			41.6 ^{1,2}
McCullough et al. (1977)	<2,130	3,166	37.0	18.2	11.9 ²	>2,740	2,962 ¹	39.0	19.2	18.5 ^{1,2}
Unger et al. (1988)	<2,130	3,235	40.0	11.6	6.0 ²	>2,740	3,058 ¹	39.5	11.5	6.5 ²
Jensen and Moore (1997)	<2,130	3,297	39.5	11.2		>2,740	3,056 ¹	39.0 ¹	14.2	
Andes										
Mazess (1965)	338				28.6 ²	3,030				52.8 ^{1,2}
Beall (1981)	600	3,410				3,860	3,140 ¹			
Haas et al. (1980)	400	3,427	39.0		10.6 ³	3,600	3,165 ¹	39.0		9.3 ³
Gonzales and Guerra- Garcia (1993)	150	3,178	39.8			4,340	2,982 ¹	38.2 ¹		
Carmen-Torres and Gonzales (1993)	150	3,180	39.2	9		4,340	2,835 ¹	38.6	12 ¹	
Himalayas										
Zamudio et al. (1993a)	1,200	3,299	39.7	7		3,600	3,236	39.8	7	
Wiley (1994)						3,600	2,764	37.8		144 ³

¹ Comparison with low altitude, $P < 0.05$.² Neonatal mortality rate = deaths within first 28 days/1,000 live births.³ Infant mortality rate = deaths within first year/1,000 live births.

residents from intrauterine growth retardation (IUGR). Nutritional, behavioral, and other pregnancy-specific characteristics are likely important in each location. Developmental factors may contribute, although whether lifelong high-altitude exposure acts to increase or decrease birth weight is unclear (Weinstein and Haas, 1977). Genetic factors are known to influence birth weight, accounting for as much as 70% of the birth-weight variation among offspring of monozygotic twins at sea level (Nance, 1976; Magnus, 1984; Vlietinck et al., 1989). The protection from altitude-associated intrauterine growth retardation (IUGR) afforded lifelong residents of high-altitude ancestry implicates genetic factors. In turn, the greater protection afforded Tibetan than Andean high-altitude natives may be due to the possession of different genetic variants. The particular maternal physiological characteristics by which genetic, developmental, or pregnancy-specific factors might operate are described in the section below.

Maternal oxygen transport responses to pregnancy. If IUGR at high altitude is due to reduced fetal-placental oxygen supply, we reasoned that the degree of growth retardation would be related to characteristics of maternal oxygen transport. Alternate possibilities are that fetal growth is impaired by limitations of placental diffusing capacity for oxygen, other nutrient supply or fetal factors inhibiting growth. Early reports indicated that the placenta at high altitude was similar in absolute size and larger in relation to fetal size than at low altitude (Sobrevilla et al., 1971). Recent studies show that the high-altitude placenta is more vascularized and has a greater diffusing capacity than the placenta at low altitude (Reshetnikova et al., 1994; Mayhew et al., 1990). Thus, impaired placental oxygen diffusing capacity is unlikely to be the source of altitude-associated IUGR.

One of the primary ways the maternal oxygen transport system responds to pregnancy is an increase in ventilation (see

Glossary). We have shown that this increase is due to elevations in circulating progesterone and estrogen levels in combination with a higher metabolic rate. These factors act on respiratory control centers in the brain and in small organelles in the neck (the carotid bodies) to raise ventilatory sensitivity to oxygen and carbon dioxide (Hannhart et al., 1989; Moore et al., 1987; Tatsumi et al., 1995). At low altitude, the increase in ventilation does not appreciably raise arterial oxygen saturation (S_aO_2) (see Glossary), since it is already nearly maximal, but does so at high altitude (Table 3). Our studies in Peru and Colorado demonstrated that the level of a woman's ventilation, hypoxic ventilatory response (HVR) (see Glossary), and S_aO_2 during pregnancy related positively to the birth weight of her infant (Moore et al., 1986, 1982a,b). In Tibet, pregnant women in our studies did not have higher levels of S_aO_2 than nonpregnant women (Table 3), nor were their levels of ventilation or S_aO_2 related to their infant's birth weight. The lack of higher S_aO_2 probably reflects the cross-sectional nature of the Tibetan study design since others have found higher values when the same women were compared in the pregnant and nonpregnant conditions (Beall et al., 1997b; Beall and Goldstein, 1990).

The major factor increasing fetal-placental oxygen supply during pregnancy is a 60-fold rise in blood flow to the uteroplacental circulation, due largely to greater uterine artery blood flow. At low altitude, this is accomplished by a doubling of uterine artery diameter, complete by mid-gestation, and a progressive rise uterine artery flow velocity (i.e. the speed which the blood travels through the vessel lumen) until term, which together cause lower extremity blood flow to be preferentially distributed to the uterine circulation (Palmer et al., 1992). At 3100 m in Colorado, the increase in uterine artery diameter in pregnancy women was only about half as great as that seen at low altitude, resulting in one-third lower uterine artery blood flow and less distribution of pelvic blood flow to favor the uterine artery (Table 3) (Zamudio et al., 1995d). Variation in uterine artery blood flow velocity correlated

positively with infant birth weight at low but not high altitude, perhaps because of variation in vessel size among the high-altitude women. Further, we observed that women who developed preeclampsia (i.e., pregnancy hypertension and proteinuria) at high altitude had even less redistribution of pelvic blood flow to favor the uterine circulation and no increase in uterine artery flow velocity near term (Zamudio et al., 1995b). This is consistent with studies at low altitude in which preeclampsia has been associated with reduced uteroplacental blood flow. A reduction in uterine artery blood flow at high altitude related consistently to the decrease in birth weight in these and previous experimental animal studies (Fig. 2).

Because babies born to Tibetan women weighed more than those of acclimatized Han newcomers at 3,658 m, we asked whether Tibetan preservation of fetal growth could be linked to increased arterial oxygen content (C_aO_2) (see Glossary) and/or greater uterine artery blood flow. In the Tibetan women, pregnancy increased maternal ventilation, but S_aO_2 was unchanged. Unlike the Colorado, Peru, and Han high-altitude residents, C_aO_2 was lower in pregnant than nonpregnant Tibetan women, due primarily to their greater fall in hemoglobin (Table 3). The Tibetan women's lower hemoglobin was likely due to greater plasma volume expansion, which may in turn have facilitated directing a larger portion of their pelvic blood flow toward the uterine artery (Moore, 1990). The greater redistribution of lower extremity flow to the uterine artery was associated with heavier birth weights in the Tibetan vs. the Han samples. Taken together, these data suggested that the Tibetans employed a strategy that maximized the increase in uterine blood flow, not C_aO_2 (Moore, 1990).

In the aggregate, these data suggest that the ways in which adequate fetal-placental oxygen delivery is maintained vary among individuals and populations, with Tibetans emphasizing an increase in uterine blood flow and the other groups protecting C_aO_2 . Since all the Andean and Tibetan women were born and raised at high altitude and there were no discernible differences be-

TABLE 3. Maternal oxygen transport during pregnancy¹

	US, low altitude ²		US, high altitude ³		Peru, high altitude ⁴		Tibetans, high altitude ⁵		Han newcomers, high altitude ⁶	
	Nonpregnant	Pregnant	Nonpregnant	Pregnant	Nonpregnant	Pregnant	Nonpregnant	Pregnant	Nonpregnant	Pregnant
Altitude (m)	<2,500	<2,500	3,100	3,100	4,300	4,300	3,658	3,658	3,658	3,658
V _E	7.1 ± 0.4	9.6 ± 0.4	8.8 ± 0.3	11.4 ± 0.3	9.5 ± 0.4	12.0 ± 0.7	10.1 ± 0.5	11.7 ± 0.3	9.1 ± 0.5	10.2 ± 0.5
VO ₂	196 ± 8	254 ± 9	199 ± 5	244 ± 5	—	—	255 ± 11	267 ± 7	233 ± 18	244 ± 18
VO ₂ /kg	3.1 ± 0.1	3.5 ± 0.2	3.1 ± 0.8	3.3 ± 0.1	—	—	5.2 ± 0.2	4.7 ± 0.1	5.0 ± 0.3	4.4 ± 0.3
HVR	124 ± 13	237 ± 26	244 ± 20	322 ± 28	23 ± 8	87 ± 17	45 ± 8	134 ± 19	44 ± 11	134 ± 16
HVR/kg	2.1	3.2	3.6 ± 0.3	4.3 ± 0.3	0.4	1.4	1.0 ± 0.2	2.3 ± 0.3	0.8 ± 0.3	2.5 ± 0.4
P _a CO ₂	38	32	31 ± 1	27 ± 1	31 ± 1	26 ± 1	31 ± 1	27 ± 1	31 ± 1	29 ± 1
S _a O ₂	94.6 ± 0.5	95.4 ± 0.4	90.9 ± 0.2	92.2 ± 0.2	82.9 ± 1.2	87.4 ± 0.4	89.0 ± 0.5	89.8 ± 0.3	86.7 ± 0.6	89.6 ± 0.5
Hgb	13.9	12.6	15.1 ± 0.2	13.8 ± 0.2	14.0 ± 0.4	13.1 ± 0.3	14.9 ± 0.2	12.6 ± 0.3	15.2 ± 0.3	14.4 ± 0.4
C _a O ₂	17.5	14.5	18.7 ± 0.2	17.3 ± 0.2	15.9 ± 0.4	15.6 ± 0.4	18.1 ± 0.3	15.5 ± 0.3	17.9 ± 0.2	17.3 ± 0.6
Blood vol	66.6	79.7	58.3 ± 1.2	69.9 ± 1.9	—	—	—	—	—	—
Plasma vol	42.6	65.9	33.7 ± 0.8	42.9 ± 1.3	—	—	—	—	—	—
C.O.	5.3	6.5	—	—	5.2 ± 0.5	5.8 ± 0.1	—	—	—	—
MAP	84	85	87 ± 1	85 ± 1	—	—	76 ± 2	85 ± 2	80 ± 2	89 ± 4
HR	74	84	81 ± 1	93 ± 2	77 ± 2	79 ± 2	76 ± 2	81 ± 2	81 ± 3	88 ± 2
UA/CI vel	1.0 ± 0.2	4.3 ± 0.4	0.9 ± 0.1	4.6 ± 0.2	—	—	—	5.5 ± 0.7	—	2.9 ± 0.4
UA vel	9 ± 2	61 ± 3	10 ± 1	69 ± 2	—	—	—	56 ± 3	—	47 ± 4
UA flow	6 ± 2	312 ± 22	8 ± 2	203 ± 48	—	—	—	—	—	—

¹ Mean ± SEM nonpregnant and pregnant values were obtained in the same women ≥3 mo postpartum and the third trimester, respectively, in the US and Peru but from different women in Tibet. V_E, ventilation, l BTPS/min; VO₂, O₂ consumption, ml STPD/min; HVR, hypoxic ventilatory response, shape parameter A; HVR/kg, HVR/kg body weight; P_aCO₂, arterial or end-tidal PCO₂, mmHg; S_aO₂, arterial O₂ saturation, %; Hgb, g/100 ml blood; C_aO₂, arterial O₂ content, ml O₂/100 ml blood; blood vol, total blood volume, ml/kg; plasma vol, plasma volume, ml/kg; C.O., cardiac output, l/min; MAP, mean arterial blood pressure, mmHg; HR, heart rate, bpm; UA/CI vel, ratio of uterine artery/common iliac artery blood flow velocity, cm/s; UA vel, uterine artery blood flow velocity, cm/s; UA flow, uterine artery blood flow, ml/min.

² US low altitude: Moore et al., 1987, unpublished data; Goodlin, 1979; Zamudio et al, 1995d; Kirschbaum, 1971.

³ US high altitude: Zamudio et al., 1993b; 1995a; Moore, unpublished data.

⁴ Peru high altitude: Zamudio et al., 1993c, 1995d.

⁵ Tibetans high altitude: Moore, 1990, unpublished data; Zamudio et al., 1993c.

⁶ Han newcomers high altitude: Moore, 1990, unpublished data.

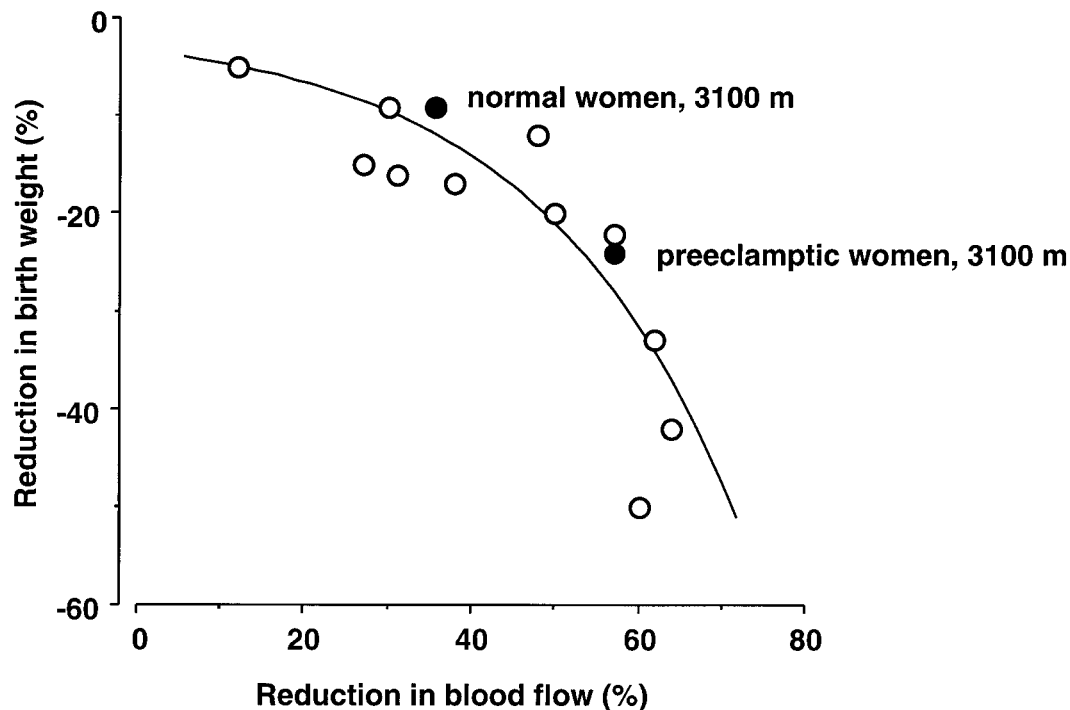


Fig. 2. Birth weight, expressed as a percentage of sea-level or low-altitude values, falls as uterine, placental, or uteroplacental blood flow diminishes in experimental animal or human studies (grouped data). Open circles are previously published values, and closed circles are from groups of normotensive or preeclamptic women studied at 3,100 m. (Reproduced from Moore 1998, with permission of the publisher.)

tween Colorado women born at high altitude vs. those moving there as adults, genetic factors are implicated in the sample differences observed. In addition, because the Tibetan women have oxygen-transport characteristics close to sea-level values and give birth to infants with the least reduction in birth weight, those factors preserving oxygen delivery closest to sea-level values appear to be the best adapted.

Neonatal, infant, and maternal mortality. Birth weight is a major determinant of infant mortality. Since mortality increases at both the lower and upper extremes of the birth-weight distribution, birth weight is considered the classic example of stabilizing selection. Given the lower birth weights generally present at high altitudes, the expectation would be that neonatal and, by extension, infant mortality would be increased. This is supported by older studies in Colorado in which mortality rates at high

altitudes were higher than those observed at lower elevations (Table 2) (McCullough et al., 1977; Lichty et al., 1957). However, current data indicate that mortality at high altitudes in Colorado has declined to nationwide levels in association with a modest increase in birth weight, a fall in percent preterm births, and likely improvements in the detection and management of complicated pregnancies (Wilcox, 1993; Unger et al., 1988). Today, as well as for as long as records are available, Peru and Bolivia have had the highest infant mortality rates of any South American country. In both countries, mortality rises with increasing elevation when all infants or only urban infants are compared (Pan American Health Organization, 1994). The Colorado data has the advantage of complete population enumeration and reasonably accurate data reporting. In South America, neonatal and infant deaths are almost certainly underreported since

registration of a birth or death requires payment and only about one-third are certified (Pan American Health Organization, 1994). No reliable infant mortality data, to our knowledge, are available from Tibet. When infant mortality between regions or countries is compared, it is important to recall that factors other than hypoxia may be involved, including infectious disease and other environmental influences as well as political factors, since infant mortality has taken on broader meaning as a yardstick for social and economic development.

Both growth retardation and preterm delivery affect infant birth weight and mortality risk. Within the range of values commonly observed, premature delivery has a much greater impact on neonatal survival than reduction in birth weight alone (Williams et al., 1982). Accordingly, the increased neonatal mortality observed previously at high altitude in Colorado was due chiefly to deaths among babies who were both growth-retarded and premature (McCullough et al., 1977). In more recent US studies, there was no difference in birth-weight-specific mortality between low and high altitudes when fetal growth retardation and preterm delivery were taken into account or for the high- compared to the low-altitude regions as a whole (Wilcox, 1993; Unger et al., 1988). In South America, the lack of complete population enumeration and gestational age information prevents determination of whether birth-weight-specific mortality is altered at high vs. low altitude. Beall (1981) reports a 170 g lower optimal birth weight (i.e., that associated with the lowest mortality rate) in a 3,860 m compared with a 600 m sample from Peru. However, since no gestational age information was available, it is possible that the lower optimal birth weight resulted from a greater contribution of growth retardation than prematurity to mortality risk at high vs. low altitude. Also, the low-altitude optimal birth weight values are considerably higher than reported by other studies (Karn and Penrose, 1957; Williams et al., 1982). In Ladakh, higher mortality risk was associated with low birth weight than in other high- or low-altitude populations (Wiley,

1994). Thus, small is not better at high (or any) altitude.

Maternal mortality in Peru and Bolivia is more than twice the South American average (Pan American Health Organization, 1994), rising from 13.2 maternal deaths per 10,000 live births at the coast to 21.5 in the 2,000–3,000 m region and to 43.1 at elevations above 3,000 m in Peru (Gonzales and Guerra-Garcia, 1993). Data from the Himalayan region are lacking. Maternal mortality is not increased at high altitude in the US, where there is ready access to medical care. However, there is greater morbidity at high altitude in Colorado and South America as measured by maternal complications of pregnancy. We have observed a three- to fourfold increase in the incidence of preeclampsia and an increase in other complications of pregnancy as well (Zamudio et al., 1993b, 1995c; Moore et al., 1982a; Jensen and Moore, 1997; Palmer et al., 1994). Data from South America are equivocal on whether preeclampsia is more common (Gonzales and Guerra-Garcia, 1993; Lopez-Jaramillo and y de Felix, 1991), and no studies have been conducted in the Himalayan region. Interestingly, we found higher blood pressures in Han than Tibetan pregnant women living at 3,658 m in Lhasa (Moore, unpublished observations). Another serious maternal complication of pregnancy, placental abruption (i.e. premature separation of the placenta from the uterine wall), is more common at high altitude in Peru. Placental abruptions were three times more common at 3,750 m in La Oroya than at sea level, occurring in 6.8% of women over 40 years and 3.4% with parity greater than 4 (Quintana et al., 1994).

The maternal and newborn data taken together support a hypothesis that increased maternal complications of pregnancy prompt more frequent preterm deliveries and in turn augment maternal as well as infant mortality. A plausible mechanism is hypoxia-related inhibition of the vasoregulatory and growth-related factors responsible for increasing uteroplacental blood flow in normal pregnancy. There is indirect support for this hypothesis from preeclamptic pregnancies at low altitude in which impaired trophoblast (i.e., the specialized epithelial cells of

the placenta) invasion of the small uterine arteries (spiral arteries) has been observed. This would be expected to lead to shallower placentation, maternal spiral arteries that retain contractile sensitivity to local and circulating substances, and lower uteroplacental blood flow (reviewed in Robertson et al., 1986). Other tests of this hypothesis are currently under way.

In summary, fertility is not reduced at high altitude, but intrauterine growth is retarded, birth weight lowered, and neonatal, infant, and maternal survival impaired except under conditions of readily accessible medical care. Our overall hypothesis, that IUGR is due to insufficient oxygen delivery to meet fetal-placental demands, is supported by consistent associations between infant birth weight and maternal ventilation, arterial oxygenation, and uterine blood flow at high altitude. The available evidence also supports the likelihood that the degree of IUGR is least in the longest resident high-altitude populations. Further, the parallels between the magnitude of IUGR and kinds of maternal oxygen transport responses to pregnancy suggest that adaptive strategies and success differ among regions. That is, Tibetans appear distinguished by lesser reductions in birth weight, lower hemoglobin concentrations, and greater blood flow distribution to the uterine circulation. The higher birth weights in native Aymara women may be accompanied by differences in oxygen transport, but these have been little studied. Of interest is that Tibetan uterine blood flow and hemoglobin levels resemble those of healthy low-altitude Colorado residents, whereas acclimatized Han newcomers are more like Colorado high-altitude women with preeclampsia.

Infant, childhood, and adolescent development

Remarkable changes in oxygen transport take place at birth. At high altitude, these are complicated by the lower oxygen tensions as well as IUGR and other conditions stemming from prenatal life. Differences among and between populations will be considered below to determine the extent to which interpopulation differences exist in in-

fant, childhood, and adolescent development.

Oxygen-transport characteristics. In the transition following birth, the lungs change from fluid- to air-filled, blood flow to the lungs increases dramatically, and vascular shunts reverse in direction and close. Oxygen plays a critical role in the postnatal transition because of its function as a pulmonary vasodilator.

At sea level, S_aO_2 is modestly lower during the first week than the 94–98% values present during neonatal life and infancy (Mok et al., 1986). At 1,610 m in Denver, Colorado, S_aO_2 in healthy, term infants was below sea-level values, averaging 92–94% from 24–48 h through 3 months of age (Thilo et al., 1991). At 3,100 m in Leadville, Colorado, S_aO_2 was lower still, especially during the first week of life (Fig. 3) (Niermeyer et al., 1993). Unlike the pattern at low altitude, S_aO_2 fell during the first week and then rose gradually to attain near-birth values at 2 and 4 months of age. The lower S_aO_2 values at 1 week were consistent with clinical signs of hypoxemia. S_aO_2 was higher in Tibetan than Han infants born at 3,658 m from birth through 4 months of age (Fig. 3) (Niermeyer et al., 1995). The neonates were similar in gestational age and Apgar scores; however, the Han had lower birth weights and higher hemoglobin and hematocrit at birth than the Tibetans. In both groups, S_aO_2 was highest in the first 2 days after birth and then declined. Whereas S_aO_2 in the Tibetan infants stabilized at 4 months to values within the range of Leadville infants, S_aO_2 in the Han declined progressively (Fig. 3). S_aO_2 in 2–5-month-old Quechua infants at 3,750 m in Peru averaged $88 \pm 3\%$ (Reuland et al., 1991), roughly similar to Tibetan values. At 4,540 m in Peru, directly measured S_aO_2 ranged from 57–75% in newborns (Gamboa and Marticorena, 1971) and remained at 74–80% throughout infancy (Sime et al., 1963).

The cause of the higher S_aO_2 in Tibetan than Han infants residing at the same elevation but differing in high-altitude ancestry likely reflects differences in ventilation and/or pulmonary blood flow, but these have not been measured. Increased ventilation

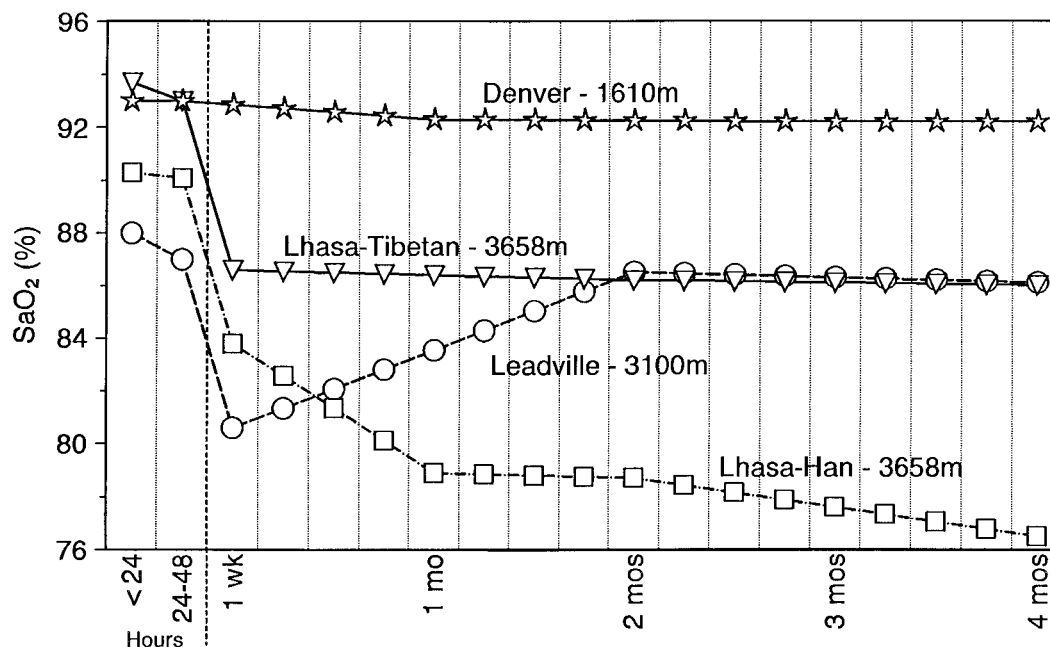


Fig. 3. Arterial oxygen saturation during quiet sleep falls with increasing altitude. Values were obtained in groups of infants studied serially. Adapted from Thilo et al. (1991) and Niermeyer et al. (1993, 1995).

would serve to decrease the oxygen-pressure gradient from the atmosphere to the alveoli and to raise arterial oxygen tensions. The accompanying fall in arterial carbon dioxide tensions could also increase pH and left-shift the oxyhemoglobin dissociation curve to raise saturation at a given oxygen pressure, but hemoglobin-oxygen dissociation curve position is unknown.

Ventilatory patterns during the neonatal period and infancy change in ways that differ at high compared with low altitude. At sea level, sleep-disordered breathing (see Glossary) occurs in the overwhelming majority (78%) of full-term neonates (Kelly et al., 1985). Its prevalence declines perhaps as early as 1 month and definitely by 5–6 months (Glotzbach and Ariagno, 1992) in response to developmental changes in central and peripheral chemoreceptors (Glotzbach and Ariagno, 1992; Matsuoka and Mortola, 1995; Lahiri et al., 1978; Barrington et al., 1987). The prevalence clearly increases at high altitudes; 100% of Leadville neonates demonstrated sleep-disordered breathing (Lubchenco et al., 1964) and a decline in

S_aO_2 (Niermeyer et al., in press). Perhaps sleep-disordered breathing is responsible for the decrease in S_aO_2 at 1 wk of age at high altitude and the consistently lower values observed during sleep compared with wakefulness throughout the first 4 months of life.

A rapid postnatal fall in pulmonary artery pressure (P_{PA}) (see Glossary) occurs in the first days of life at sea level, which is important for achieving closure of atrial and ductal shunts (Emmanouilides et al., 1964). In healthy, term infants at 3,100 m, all of whom received supplemental oxygen during the first 24–48 h, P_{PA} indices were normal to moderately elevated during the first week of life and fully normal at 2–4 months (Niermeyer et al., 1993). At higher altitudes without supplemental oxygen, the postnatal fall in P_{PA} is prolonged or fails to occur. Newborns at 4,540 m in Peru showed persistence of near-systemic P_{PA} for several days following birth (Fig. 4). Administration of 100% oxygen at 72 h dramatically lowered P_{PA} to near sea-level values. Elevated P_{PA} and pulmonary vascular resistance were confirmed by right heart cardiac catheterization in

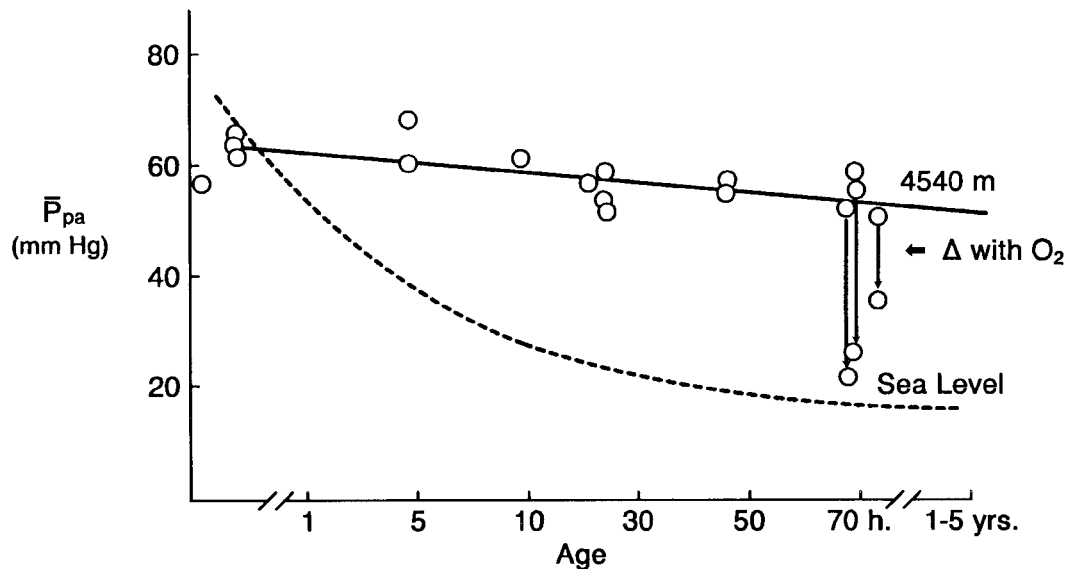


Fig. 4. The fall in pulmonary arterial pressure (P_{PA}) in neonates at sea level is greater than at 4,540 m in Peru. Supplemental oxygen restores values in high-altitude neonates to sea-level values. Adapted from Gamboa and Marticorena (1971). Values from individual babies are shown as open circles; lines represent averaged data.

infants and children under 5 years of age at 4,330 m and 4,540 m in Peru (Sime et al., 1963). Further support for delayed or, in some cases, absent postnatal regression of the fetal pulmonary vascular pattern comes from histological observations in South America of more muscularized pulmonary arteries or arterioles and more frequent occurrence of patent ductus arteriosus (Arias-Stella and Saldana, 1962; Alzamora-Castro et al., 1960; Gamboa and Marticorena, 1972). An increased prevalence of atrial septal defect and patent ductus arteriosus has also been observed in Han and Tibetan infants in Qinghai Province of China (the northern portion of the Tibetan plateau), rising from near zero at sea level to more than 5% at 4,500 m (Miao et al., 1988).

A syndrome of pulmonary hypertension and right heart failure termed subacute infantile mountain sickness has been described in five infants and six older children in Leadville, Colorado, and 15 infants or children at 3,658 m in Tibet (Khoury and Hawes, 1963; Sui et al., 1988). The infants or children in Tibet died between 3 and 16 months of age with signs of pulmonary hypertension and right heart failure. All

were male; 14 were Han, and one was Tibetan. All but two were born at low altitude and brought to Lhasa at an average of 2 months before the onset of disease symptoms (e.g., shortness of breath, cough, cyanosis, facial edema, sleeplessness, and irritability). On autopsy, the small pulmonary arteries and arterioles were more muscularized, and the right ventricles of the heart were markedly enlarged in comparison with a group of similarly aged Tibetan infants and children who died of noncardiopulmonary causes.

In summary, newborns at high altitude experience a slower transition from fetal to mature patterns of cardiopulmonary function. S_aO_2 is lower than at sea level, particularly in populations that have recently migrated to high altitude. Periodic breathing appears to be more common and may contribute to lower S_aO_2 during sleep. The postnatal fall in P_{PA} is markedly slower at higher altitudes but only modestly delayed at more intermediate altitudes where supplemental oxygen is used routinely. Whereas fetal cardiovascular patterns persist into childhood in South America and Han migrant populations in Tibet, histologic data in native Ti-

betan infants suggest a more rapid involution of fetal patterns. A possible reason for this difference between Tibetan vs. Han children is their better-sustained S_aO_2 during early infancy.

Growth and nutrition. Growth at high altitude is a product of genetic and/or developmental factors acting in concert with nutrition, levels of habitual activity, and other socioeconomic and environmental characteristics. Generally, decreased growth in utero is sustained postnatally at high altitude. In Andean samples, a consistent reduction in length and weight from birth to 2 years has been observed at high compared with low altitude (Haas, 1976). A comparison of highland and coastal children in Ecuador found that shorter stature in the highlands was due to diminished linear growth velocity within the first 6 months (Leonard et al., 1995). Delayed growth in Andean highlanders continues during childhood and adolescence, resulting in a 1–2 year lag in height and a less pronounced adolescent growth spurt. Adolescents grow for about 2 years longer or until 22 years of age, but adult stature remains shorter than at low altitude (Beall et al., 1977; Beall, 1982; Frisancho and Baker, 1970; Frisancho, 1969; Mueller et al., 1978a,b).

The growth failure at high altitude in South America is consistent with that seen among impoverished populations worldwide (Haas, 1976), suggesting the involvement of nutritional factors. This is supported by observations that upper socioeconomic status (SES) children in Nuñoa, Peru, were taller and heavier than lower SES children (Leonard and Thomas, 1989). Over the past two decades, the age at which peak growth velocity was attained and growth completed declined in above-average SES adolescents but remained unchanged in lower SES adolescents in the southern Peruvian Andes (Leatherman et al., 1995). Comparisons in Bolivia found no difference in anthropometric characteristics between highland and lowland boys when the comparisons were controlled for SES and nutritional status. Boys from a low SES background at high and low altitude were marginally undernour-

ished and showed a growth delay of approximately 2 years (Obert et al., 1994).

The pattern of growth retardation in the Himalayas also suggests the influence of nutritional or other socioeconomic factors (Kolsteren et al., 1990; Malik and Pandey, 1993; Pawson, 1977). There do not appear to be appreciable differences in growth retardation among Tibetan, Han, and Hui (a central Asian group) male adolescents at 3,200 m and 4,300 m in Qinghai Province, but all groups had average body weights at or below the National Center for Health Statistics (NCHS) fifth percentile, and average height was at or slightly above the fifth percentile (Weitz et al., 1995). Rural Tibetans fell below the NCHS standards in height and weight by 4–6 months in both sexes (Kolsteren et al., 1990). In the urban Lhasa valley, weight-for-height was normal, but weight and height for age were at the lower range of the NCHS standards. Weight-for-height in Lhasa dropped below NCHS standards at two time points: one around 6 months, perhaps reflecting the increased importance of supplemental foods at this age, and the second at 1–2 years, when children begin to walk and to depend more on adult foods (Kolsteren et al., 1990).

As mentioned above, Han infants often remain with extended family in lowland China until about 2 years of age, at which time they are brought back to Tibet. Newly arrived Han children showed poor appetite, diarrhea, and intestinal malabsorption, all of which can adversely affect growth (Kolsteren et al., 1990). The Han children had markedly lower body weights by age 3 than the native Tibetan children, both rural and urban, despite the generally favored economic circumstances of the Han compared to the Tibetan population.

Enlarged chest dimensions (particularly depth) and accelerated chest development, despite generally smaller body size, have been reported in numerous studies at high altitude. Since persons of Andean (Quechua) ancestry born and raised at low altitude also have enlarged chest dimensions (Melton, 1992; Greksa et al., 1994), larger chest dimensions may be a fixed genetic trait in this population. Chest dimensions have significant heritability (see Glossary) among the

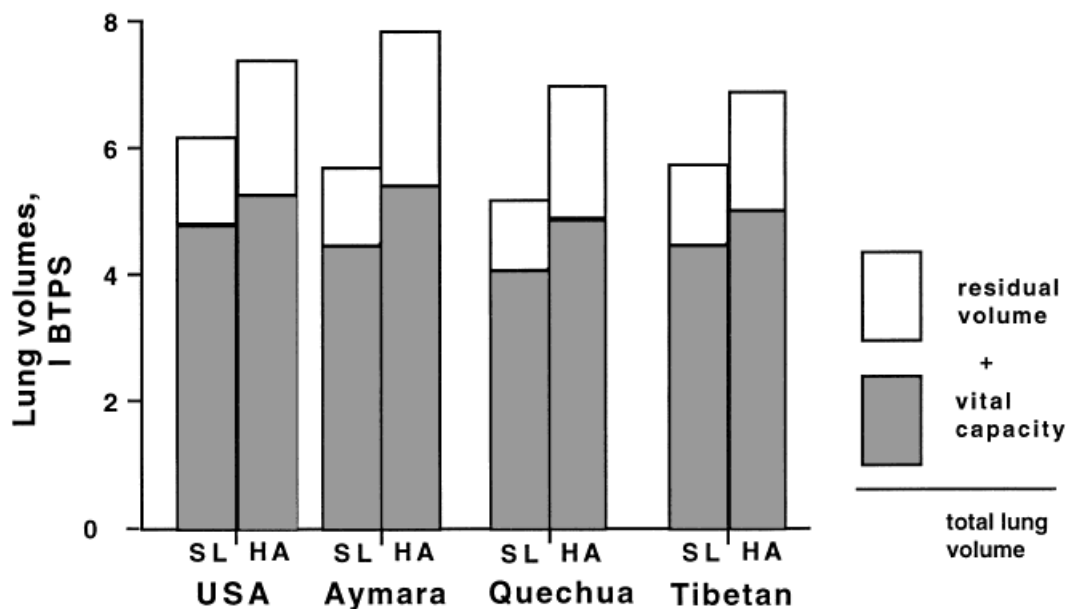


Fig. 5. Total lung volume is the sum of residual volume and vital capacity (liters BTPS). Open bars are predicted values for sea-level (SL) residents of the age and height of the groups of lifelong high-altitude (HA) residents in Colorado at 3,100 m (Cockrell and Poston, 1996; Esterman et al., 1996), South America at 3,600–4,540 m (Greksa et al., 1994; Broughton-Pipkin et al., 1989), and Tibet at 3,658 m (Droma et al., 1991).

Quechua and Aymara, and heritability was greater at high altitude (Kramer, 1992). This has been interpreted as being due to natural selection acting to increase the representation of genes increasing chest dimensions at high altitudes (Ahn, 1992). Phenotypic plasticity may also be involved since genes coding for accelerated chest development might be preferentially expressed at high altitude.

It is important to recall that lung volumes (see Glossary), not chest dimensions, have functional significance; at high altitude, greater lung volumes are associated with increased surface area for gas exchange, decreased alveolar-arterial oxygen diffusion differences, and better-maintained S_aO_2 during exercise. While an equivalence is often assumed, chest dimensions are not the same as lung volumes since the chest contains structures other than the lung and larger lung volumes may be accommodated by a lower diaphragm, not a larger rib cage. Despite the large number of studies of chest dimensions, there is a paucity of complete lung volume measurements. However, exist-

ing data clearly demonstrate that lung volumes are increased worldwide at high compared with low altitude, whether the high-altitude groups are compared with low-altitude US standards or with samples drawn from newcomers living at the same altitude (Fig. 5). Residual volume increases the most, but vital capacity and total lung volume are also enlarged at high altitude (Fig. 5). Adolescents of Aymara and mestizo ancestry have modestly (~4%) larger vital capacities when adjusted for differences in body size than similarly aged adolescents of European ancestry born and raised at high altitude (Greksa et al., 1988).

Past debate has centered on whether lung volumes are equally enlarged in Himalayan and Andean populations. However, as demonstrated in Figure 5, Tibetan high-altitude residents clearly have enlarged lung volumes. Lung volumes are also increased in young Bod girls at high altitude in Ladakh, Jammu, and Kashmir, India, compared with their lowland counterparts (Malik and Pandey, 1993) and in boys between 5 and 18 years at high altitude in Himachal Pradesh

(Malhotra, 1986). Rigorous determination of whether the magnitude of increase varies in the Andean, Himalayan, and Rocky Mountain regions is hampered by substantial interpopulational variation in body size and disagreement regarding the best reference population. Thus, the information summarized in Figure 5 demonstrates that if differences are present, they are of modest proportion.

Larger lung volumes result from exposure to high altitude during growth and development, as they cannot be acquired in adult animals spending an equivalent period of time at high altitude (Johnson et al., 1985). The increase in each lung volume is present by early adolescence (age 11), with residual volume enlarging progressively from 11–19 years (Greksa et al., 1994). Frisancho et al. (1997) recently examined the environmental, developmental, and genetic contributions to lung volumes in Bolivian high-altitude residents of low- and high-altitude ancestry. They found that growth and development at high altitude accounted for approximately 25% of the increase in vital capacity and residual volume among males but, interestingly, not among females (Frisancho et al., 1997). Genetic factors accounted for an additional 25% of the variability. Occupational characteristics associated with rural high-altitude residence further raised vital capacity but not residual volume. Thus, these authors concluded that environmental factors (occupation, body composition) exerted greater influence on increasing vital capacity than developmental characteristics, whereas both developmental and genetic factors raised residual volume, at least in males (Frisancho et al., 1997).

Taken together, these studies indicate that childhood and adolescent growth at high altitude is characterized by the universal development of enlarged lung dimensions and by overall body growth retardation compared to sea-level standards. Nutritional stress plays an important role, especially in rural populations. However, even when nutritional factors are optimized, some degree of growth retardation appears present at high altitude.

Exercise performance. Exercise performance in children at high altitude demonstrates the influences of hypoxia as well as nutritional status, developmental, and genetic factors. Greksa et al. (1985) found that 11–12-year-old healthy, well-nourished Aymara or upper SES European boys in La Paz, Bolivia, had about a 10% reduction in maximal exercise capacity (VO_2max) (see Glossary) when compared with their low-altitude counterparts. Obert et al. (1993) found that VO_2max per kilogram of body weight in highland boys was also 11% lower than lowland boys. SES-related differences in body size and weight raised VO_2max at high and low altitude. When VO_2max was normalized per kilogram of lean body mass, differences disappeared between the high and low SES groups at a given altitude but remained between altitudes for a given SES group. Maximal power during a force-velocity test and mean power during a 30 s Wingate test were higher in upper SES than lower SES boys, probably reflecting mild malnutrition in the latter. The authors concluded that a marginal state of malnutrition did not affect VO_2max but led to lower power in prepubertal males at both high and low altitude (Obert et al., 1993). A similarly designed study of prepubertal Bolivian girls supported these conclusions (Blonc et al., 1996).

Frisancho et al. (1995) demonstrated that persons born and raised at 3,750 m in La Paz had greater VO_2max than those who acclimatized during adulthood. Younger age, particularly before age 10, related to greater VO_2max . Overall, developmental influences accounted for 25% of the variability in VO_2max among high-altitude residents, and genetic factors accounted for an additional 25%.

In summary, high-altitude residence reduces VO_2max in children in a fashion that is relatively independent of nutritional and other SES influences. Being born and raised at high altitude as well as genetic factors serve to restore VO_2max toward sea-level values.

Illnesses. In addition to the effects of hypoxia and nutrition, the presence of childhood diseases can exert important influences on

exercise performance and growth. There are several ways in which the environmental conditions associated with high altitude interact with childhood illnesses.

Some health problems in children are uniquely related to high altitude. One such problem is reascent high-altitude pulmonary edema (HAPE) which occurs, rarely, in children after sojourn at low altitude (Scoggins et al., 1977). Repeated episodes can occur in the same child and tend to run in families. Cardiac catheterization in seven Leadville, Colorado, children (3,100 m) after recovery from HAPE showed greater P_{PA} response to hypoxia than in control children and right ventricular hypertrophy by ECG criteria (Fasules et al., 1985). Reascent HAPE has been reported in 4–19-year-old residents of Bogotá, Columbia, at 2,640 m (Ucrois et al., 1994). Data from the Tibetan plateau suggest an incidence of 1.5% in Han children compared to approximately 0.2% in Tibetans (Wu et al., 1994).

Other health problems in children are influenced by cultural responses to the high-altitude environment. Rickets reach a peak incidence of 21% in the 18- to 35-month age group in the Lhasa region. Though there are ample hours of sunshine, the cultural responses to the climate (i.e., multiple layers of clothing and thick-walled houses with small windows) limit sunlight exposure. Lower prevalence in young children likely reflects the protective effects of breast milk, and older children play outside even during winter. Cultural factors such as exposure to smoke from cooking fires and crowded living conditions likely promote respiratory diseases and exaggerate hypoxemia, particularly in colder months (Kolsteren et al., 1990). Malnutrition and lack of health care make diarrheal and respiratory illnesses major contributors to child mortality at high altitude (Luerssen, 1994).

Finally, some child health “problems” may result from definitions being applied with inappropriate but well-intentioned criteria. The World Health Organization’s definition for childhood anemia adds 0.57 g hemoglobin for every 1,000 m to the sea-level lower limit of normal (13.03 g/100 ml whole blood) (Kolsteren et al., 1990). Using these criteria,

49% of Tibetan and 25% of Han children are anemic. It is likely, however, that these criteria overestimate anemia in the Tibetan group. Tibetan hemoglobins are normally distributed in most age groups, with mean values being very close to the corresponding sea-level norm. Using sea-level criteria, the overall prevalence of anemia becomes 12% in Tibetan children from 6 months to 7 years of age. This information supports findings in adults and suggests that the Tibetan population does not respond to altitude with as great an increase in hemoglobin as do the Han (Kolsteren et al., 1990). Consequently, it may be inappropriate to apply the same disease criteria to children from different populations even though they reside at the same altitude.

In summary, the effects of hypoxia on infant, childhood, and adolescent development vary among and within high-altitude regions. Common to all regions is lower S_aO_2 , retention of fetal cardiopulmonary characteristics, delayed growth, enlarged lung volume, and diminished exercise capacity. Inadequate nutritional resources exaggerate postnatal growth retardation. Tibetan infants have higher S_aO_2 , less muscularized pulmonary arterioles, and better neonatal cardiopulmonary transition than Han living at the same altitude. It is not clear whether growth retardation is less marked in Tibetan than Andean highlanders; definitive interpretation requires studies of energy expenditure and substrate utilization. Likewise, existing data are insufficient to determine whether differences exist between Tibetan and Andean infants in S_aO_2 , cardiopulmonary characteristics, and exercise capacity. Hypoxia prompts diseases such as reascent HAPE and exacerbates others, such as acute respiratory infection and diarrheal diseases, particularly when combined with the environmental and cultural characteristics frequently encountered at high altitude.

Adulthood and old age

During adulthood, members of one generation function as the primary producers of food and other resources required for their

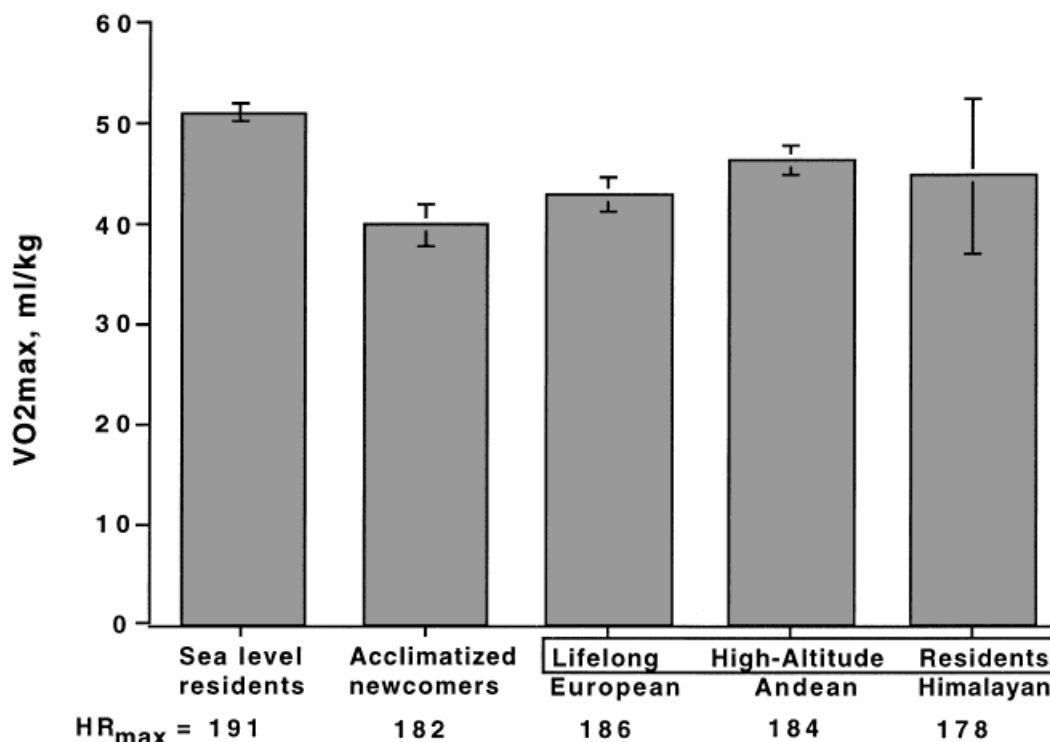


Fig. 6. In studies meeting the criterion for maximal oxygen consumption (VO₂max), exercise capacity was reduced in acclimatized newcomers as well as lifelong high-altitude residents when compared to values from a large series of normal sea-level residents (Vogel et al., 1986). Lifelong high-altitude residence appears to confer some recovery in VO₂max. Relative to acclimatized newcomer values, exercise capacity increased 8% in lifelong European high-altitude residents, 16% in Andean residents, and 12% in Himalayan natives. Average maximal heart rates (HR_{max}) (beats/minute) are also

shown. All data are group averages. Data for lifelong European high-altitude residents of 3,100–3,830 m were reported by Grover et al. (1967), Dempsey et al. (1971), and Mazess (1969). Andean residents of 3,400–4,540 m are taken from Frisancho et al. (1973), Mazess (1969), Kollias et al. (1968), Vogel et al. (1974), Elsnier et al. (1964), Favier et al. (1995), and Schoene et al. (1990). Data from Himalayan residents of 3,658–4,700 m were published by Sun et al. (1990a), Ge et al. (1994), and Curran-Everett et al. (1992).

own, their children's, and perhaps their parents' and even grandparents' survival. This requires work. Hence, work (exercise) performance is useful for evaluating adult high-altitude adaptation. In this section, we examine exercise performance in lifelong Rocky Mountain, Andean, and Himalayan high-altitude residents and in acclimatized newcomers, the control group with whom lifelong high-altitude residents have been most frequently compared. Considered are the parameters of oxygen transport influencing exercise performance in these groups. We conclude with a consideration of chronic mountain sickness and other diseases which can substantially impair the adult's ability to survive at high altitude.

Exercise performance. Exercise capacity (VO₂max) is reduced at high altitude (Fig. 6) (Matheson et al., 1991). Lifelong high-altitude residence partially restores VO₂max as the result of developmental and possibly genetic factors (Frisancho et al., 1973, 1995; Sun et al., 1990a). In comparison with acclimatized newcomers, VO₂max is 8% higher in lifelong natives of European ancestry, 16% higher in native Andean residents, and 12% higher in Himalayan natives (Fig. 6). Native high-altitude residents also appear to be less affected than acclimatized newcomers by change in altitude; across the same altitude range, ascent decreased VO₂max 15% in sea-level residents, whereas descent increased VO₂max half as much (8%) in high-

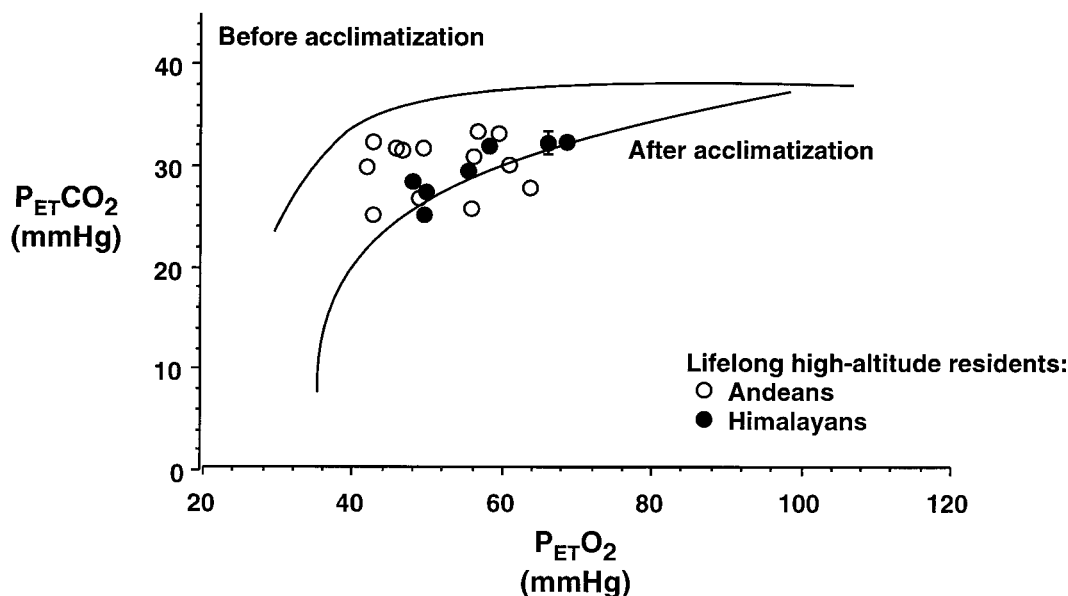


Fig. 7. End-tidal PCO_2 ($P_{ET}CO_2$) falls with decreasing end-tidal PO_2 ($P_{ET}O_2$) at high altitude in acclimatized newcomers (after acclimatization line) reflecting increase in alveolar ventilation. Lifelong Himalayan high-altitude residents (filled circles) have higher levels of alveolar ventilation than Andean (open circles) in most studies. Circles represent average values for groups of persons residing at a given altitude. Bars are standard errors. (Reprinted from Zhuang et al., 1993a, with permission of the publishers.)

altitude natives (Favier et al., 1995; Hochachka et al., 1991).

Exercise efficiency (see Glossary) is increased in some but not other studies of Andean and Himalayan high-altitude natives compared with acclimatized newcomers. Efficiency was nearly 30% greater in native Quechua highlanders (Hochachka et al., 1991) and has also been reported to be greater in Tibetans than acclimatized lowlanders (Ge et al., 1994; Curran-Everett et al., 1992; Barleon et al., 1996).

Characteristics of oxygen transport. Greater exercise capacity or efficiency in high-altitude natives likely reflects factors serving to restore oxygen transport toward sea-level values. These factors can be divided into those increasing oxygen content of the blood, raising blood flow to the working muscle and other tissues, or augmenting the amount of oxygen extracted by the tissues.

Oxygen content of the blood is determined by ventilation, alveolar-arterial oxygen difference [(A-a)DO₂] (see Glossary), hemoglobin-oxygen affinity (see Glossary), and hemo-

globin concentration (see Glossary). Ventilation rises after ascent (ventilatory acclimatization) due to hypoxic stimulation which gradually (over days) overcomes the inhibitory effects of hypocapnia. Because ventilation measured at the mouth reflects the movement of air in gas-exchange as well as non-gas-exchange regions of the lung and can also reflect variation in metabolic rate, ventilation is best measured as alveolar ventilation per unit of carbon dioxide production or alveolar ventilation. Fortunately, this is easily expressed as the arterial or end-tidal PCO_2 at a given PO_2 and visualized as a plot relating these two variables (Fig. 7). A long-standing concept has been that lifelong high-altitude residents have lower levels of alveolar ventilation than acclimatized newcomers as the result of blunting of HVR. This may be true for Rocky Mountain residents (Dempsey et al., 1971; Weil et al., 1971) and some Andeans (Severinghaus et al., 1966), but it has recently been challenged with respect to Himalayan highlanders (Zhuang et al., 1993a) or for Andean high-altitude residents when complete popu-

lations are studied (Beall et al., 1997a). Earlier reports were based on small samples and studies of newcomers that had been exposed to a range of altitudes (Lahiri, 1968; Lahiri and Milledge, 1967; Santolaya et al., 1989). Most (Zhuang et al., 1993a; Huang et al., 1981; Hackett et al., 1980) but not all (Santolaya et al., 1989) recent studies involving larger and more representative Himalayan samples find equivalent levels of effective alveolar ventilation in high-altitude residents and acclimatized newcomers (Fig. 7). It is of interest that nearly all the Himalayan high-altitude points lie closer to the after-acclimatization curve than the Andean ones and lie below the Andean points, indicating higher effective alveolar ventilation in the Himalayan than Andean highlanders (Zhuang et al., 1993a). This conclusion is supported by direct comparisons of ventilation in large numbers of Aymara and Tibetans living at the same altitude (Beall et al., 1997a).

An important factor influencing ventilation at high altitude is the hypoxic ventilatory response (HVR) (Huang et al., 1984; Lahiri et al., 1969; Weil et al., 1971; Milledge and Lahiri, 1967; Severinghaus et al., 1966). Consistent with the maintenance of higher ventilation, lifelong high-altitude Tibetan residents have HVRs at least as great as acclimatized newcomers, greater than newcomers who migrated to high altitude as children, and greater than Andean residents of similar altitudes (Zhuang et al., 1993a; Huang et al., 1981; Hackett et al., 1980; Beall et al., 1997a). The higher HVRs in Tibetans than Andeans are likely due to innate, possibly genetic factors, although developmental alterations resulting from differences in intrauterine or neonatal oxygenation have not been excluded. Twin studies at low altitude demonstrate that a significant portion of the variation in HVR is due to genetic factors (Collins et al., 1978; Kawakami et al., 1982). At high altitude, the studies of Beall et al. (1997a) also demonstrate significant, higher heritability in Tibetans (34%) than Andeans (22%), leading the authors to suggest that natural selection has acted to increase the frequency of genes for high ventilation and maintain HVR in the Tibetans, whereas such genetic variants

have been lost (or were never present) in the Andean population.

Alveolar-arterial oxygen diffusion difference $[(A-a)DO_2]$ and hemoglobin-oxygen affinity (see Glossary) affect the pressure and amount of oxygen in the blood. High-altitude Tibetan, Andean, and Rocky Mountain natives have narrower $(A-a)DO_2$ than acclimatized newcomers (Fig. 8), which permits natives to better maintain S_aO_2 across a broad range of exercise levels. Narrower $(A-a)DO_2$ is likely due in part to larger lung volumes yielding greater surface area for gas exchange. There are no apparent differences in $(A-a)DO_2$ among the various high-altitude regions (Fig. 8). Hemoglobin-oxygen affinity is determined by hemoglobin structure and effectors of hemoglobin-oxygen binding (pH, temperature, red blood cell concentrations of 2,3-diphosphoglycerate and adenosine triphosphate). Increased affinity left-shifts dissociation curve position (lower P_{50}) and raises S_aO_2 at a given arterial PO_2 . There are no reports of electrophoretic or DNA sequence hemoglobin variants in adult, human high-altitude residents, but, if present, they do not appear to affect hemoglobin-oxygen affinity. Andean and Himalayan data indicate that P_{50} is fully normal by sea-level standards (Moore et al., 1992; Samaja et al., 1979). Most studies have been performed at rest; Tibetans at near-maximal exercise also have normal P_{50} , and in vivo P_{50} rises modestly to 28.4 ± 0.5 mmHg as the result of mild acidosis (arterial pH of 7.38 ± 0.01) (Moore, unpublished observations).

S_aO_2 exhibits a pattern of inheritance consistent with a simple, single, autosomal locus with dominance in Tibetans but not Andeans (Beall et al., 1994, 1997b). It is not clear what this gene (or group of closely linked genes) is.

C_aO_2 , or the amount of oxygen in the blood, is best measured directly but is more often calculated from S_aO_2 and hemoglobin concentration. Hemoglobin concentration at a given altitude has generally been reported to be lower in Himalayan than Andean highlanders, although there is considerable overlap between the two groups (Beall et al., 1990; Winslow et al., 1990). Lower hemoglobin may result from a lesser hypoxic stimu-

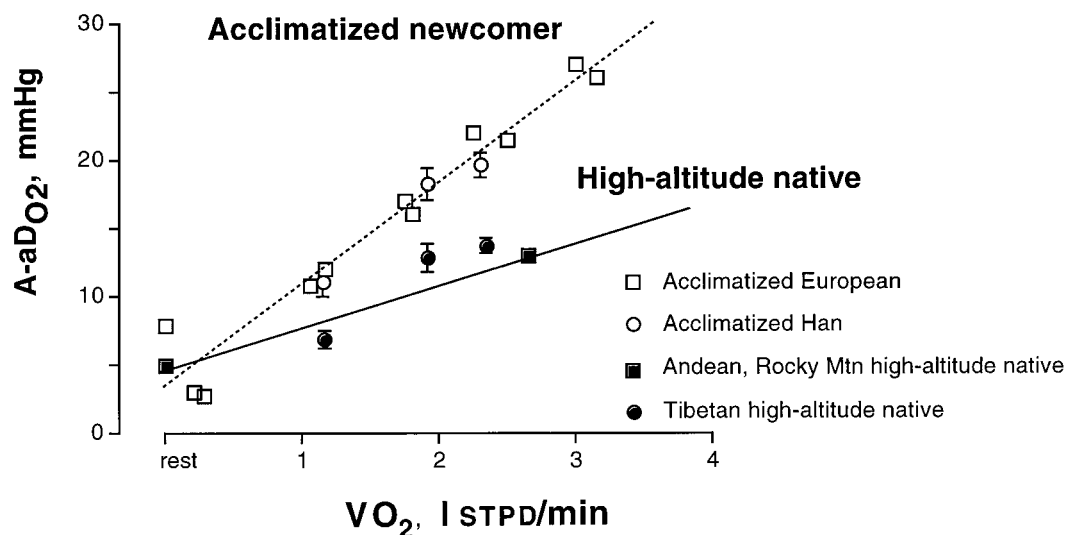


Fig. 8. The alveolar-arterial oxygen difference [(A-a)DO₂] is lower in high-altitude natives than acclimatized lowlanders (from Zhuang et al., 1996). Andean, Rocky Mountain, and Himalayan values are similar in relation to levels of oxygen consumption (VO₂). Circles and squares are average values for residents of a given altitude; standard error bars are shown when available. (Reproduced from Zhuang et al., 1996, with permission of the publisher.)

lus, due perhaps to better-maintained ventilation during the day or night and/or a lesser erythropoietic response (Winslow et al., 1990). Other factors may be involved, including developmental regulation of hemoglobin production, red blood cell destruction, and other influences on oxygenation, including chronic lung disease (Hsu et al., 1988; Frisanch, 1988).

Several lines of evidence suggest that natives may have greater cardiac outputs (see Glossary) during exercise than acclimatized newcomers. Existing data do not support higher heart rates at maximal exercise (Fig. 6) but rather suggest lower values and greater reliance on parasympathetic tone in high-altitude natives (Zhuang et al., 1993b; Savard et al., 1995; Hartley et al., 1974). Greater stroke volume is supported by larger heart volumes in young Tibetan men than similarly-sized and aged, healthy acclimatized newcomers at 3,658 m (604 ± 21 vs. 550 ± 24 cm³ or 377 ± 11 vs. 347 ± 12 cm³/m² body surface area [Moore, unpublished data]). Native Tibetans during exercise at 3,658 m increased preload normally and raised their stroke volume more than Colorado or Peruvian high-altitude natives (Groves et al., 1993; Hartley et al., 1967;

Banchero et al., 1966). Pulmonary arterial pressure and resistance were remarkably low and unresponsive to added hypoxia in comparison with lifelong Rocky Mountain or Andean high-altitude natives (Fig. 9) (Groves et al., 1993). Consistent with the absence of hypoxic pulmonary vasoconstriction were observations in Tibetan men at 3,600 m in Ladakh showing a lack of smooth muscle in the small pulmonary arteries (Gupta et al., 1992). Similar findings have been reported in the yak (Durmowicz et al., 1993; Heath et al., 1984), snow pig (Sun et al., 1989), and llama (Banchero et al., 1971), species generally considered to be genetically adapted to high altitude. Thus, existing data suggest that well-maintained myocardial contractility and low pulmonary vascular resistance permit Tibetans to attain high cardiac outputs during exercise. Determining whether values at an equivalent workload are higher than in Andean or Rocky Mountain high-altitude residents requires larger, well-controlled comparisons using reliable techniques.

Tibetans may also have better blood flow distribution to high-demand organs such as the brain and, as mentioned above, during pregnancy, the uterus. In comparison with

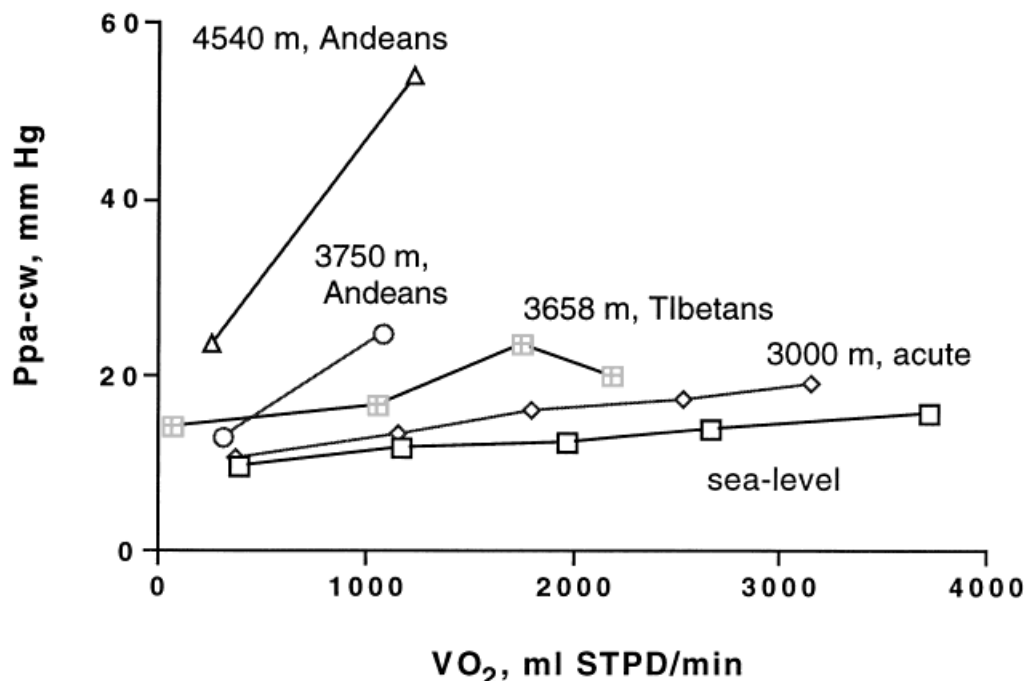


Fig. 9. The pressure gradient across the lung ($P_{PA}-P_{CW}$, pulmonary arterial pressure - pulmonary capillary wedge pressure, mm Hg) changes little with increasing oxygen consumption (VO_2 , ml STPD/min) in groups of sea-level residents (open squares) (Bebout et al., 1989; Wagner et al., 1986), sea-level residents after acute exposure to

3,000 m (open diamonds) (Bebout et al., 1989; Wagner et al., 1986), and Tibetan residents of 3,658 m (squares with crosses) (Groves et al., 1993) but rises markedly in Andean lifelong residents of 3,750 m and 4,540 m (open triangles) (Lockhart et al., 1976; Banchero et al., 1966).

acclimatized newcomers, young Tibetan men maintained higher cerebral blood flow during exercise, particularly at maximal effort (Huang et al., 1992). Nuclear magnetic resonance (NMR) imaging studies in Himalayan natives and European elite climbers also showed high-altitude natives to have fewer changes indicative of brain damage and poor perfusion despite more frequent exposure to extreme altitudes without supplemental oxygen (Garrido et al., 1996).

Factors raising tissue oxygen extraction have been less thoroughly studied than those increasing blood oxygen content or blood flow. The relationship between the difference in arterial-mixed venous oxygen content ($C_{aO_2} - C_{vO_2}$) (see Glossary) and cardiac output provides a convenient measure of tissue oxygen extraction (Fig. 10). Compared with sea level, acute hypoxia lowered and acclimatization raised $C_{aO_2} - C_{vO_2}$ per unit blood flow, probably as the result of

changes in arterial oxygen content. A further increase to within the range of sea-level values occurred in Rocky Mountain, Andean, and Tibetan high-altitude natives (Fig. 10), which could have been due to increased tissue blood flow or to lower mixed venous oxygen content. Because only the Tibetan high-altitude natives were studied across the full range of exercise (cardiac output) levels, it is not possible to determine whether oxygen extraction differs among the regional high-altitude populations.

Factors which can increase tissue oxygen extraction include greater skeletal muscle capillarity, mitochondrial volume density, oxidative enzyme capacity, or reliance on anaerobic metabolism. Sherpa mountaineers have normal skeletal muscle capillarity, low mitochondrial volume, and lower mitochondrial oxidative capacity (Kayser et al., 1991, 1996; Matheson et al., 1991). Greater reliance on anaerobic metabolism is not

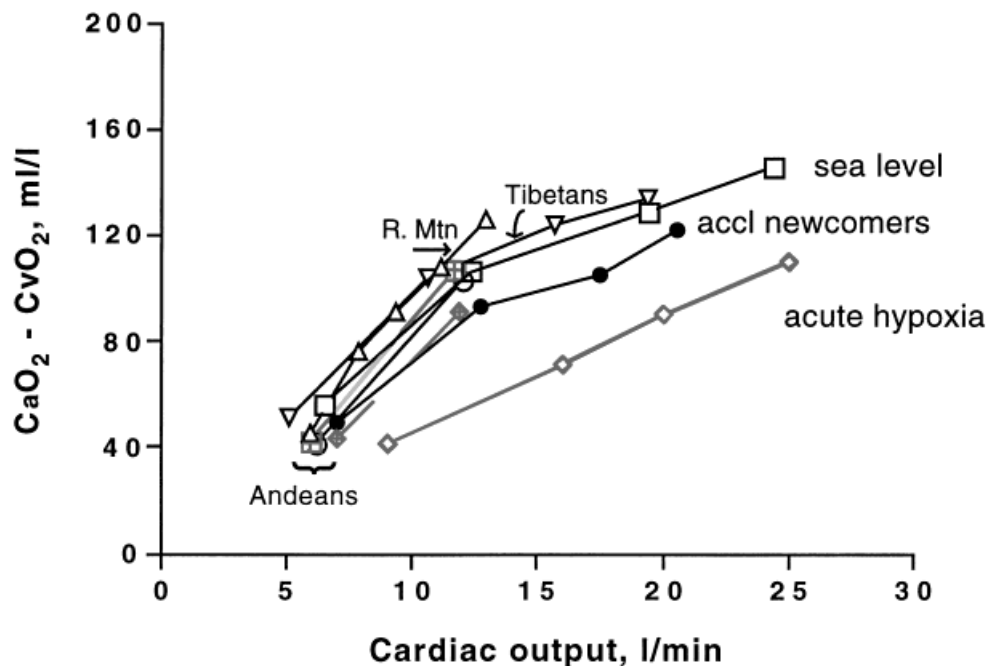


Fig. 10. The arterial-venous difference in oxygen content ($C_{aO_2} - C_{vO_2}$, ml O_2 /liter whole blood) rises with increasing cardiac output during exercise in groups of sea-level residents (open squares) (Bebout et al., 1989; Wagner et al., 1986). The difference is narrowed for a given cardiac output in groups of sea-level residents after acute exposure to 3,000 m (open diamonds) (Bebout et al., 1989; Wagner et al., 1986) and in groups of

m (open circles) (Bebout et al., 1989). Groups of lifelong high-altitude residents of Tibet (downward pointing triangles) (Groves et al., 1993); the Andes (squares with crosses (from Sime et al., 1971); diamonds with crosses (from Lockhart et al., 1976); solid circles (from Banchemo et al., 1966); and Colorado (upward pointing triangles) (Hartley et al., 1967) more closely resemble sea-level residents.

apparent in lifelong high-altitude natives or acclimatized newcomers compared with sea-level residents (Ge et al., 1994; Hochachka et al., 1991). Hochachka et al. (1991) have advanced the idea that closer coupling of ATP supply and demand enables more efficient mitochondrial oxygen utilization. NMR studies of muscle metabolism conducted at sea level showed that Quechua natives accomplished greater calf muscle work with similar or reduced perturbations in phosphorylation potential, phosphocreatine, or ATP concentration than sedentary, endurance, or power-trained athletes (Hochachka et al., 1991; Matheson et al., 1991). Alternatively, Kayser et al. (1991) have suggested that a shorter oxygen diffusion path, greater oxygen conductance, or increased tissue oxygen stores as the result of elevated myoglobin or other oxygen-binding pigments may be involved.

In summary, maximal exercise capacity appears restored toward sea-level values in lifelong high-altitude residents compared with acclimatized newcomers. Tibetans exhibit greater alveolar ventilation and higher HVR, which are likely to help maintain arterial oxygenation at rest as well as during exercise. All three regional groups demonstrate decreased $(A-a)DO_2$, due probably to enlarged lung volumes. One of the most decisive differences observed is the Tibetans' low pulmonary arterial pressures (Groves et al., 1993). The consequent reduction in afterload to the right heart may permit the Tibetans to achieve a greater rise in cardiac output during exercise than acclimatized newcomers or other high-altitude natives. Tissue-related characteristics influencing tissue oxygen extraction in high-altitude natives warrant additional investigation.

Chronic mountain sickness (CMS) and other illnesses. Chronic mountain sickness (CMS), also called Monge's disease or excessive polycythemia, is an example of adaptive failure (Monge, 1948). It occurs among adults and older-aged persons after prolonged residence at high altitude and can be eventually fatal unless treated by phlebotomy, respiratory stimulants, or descent. Diagnosis is based on hemoglobin or hematocrit values above the normal range for that altitude in the absence of chronic lung or left-sided heart disease (Monge et al., 1992; Kryger et al., 1978c). Symptoms of headache, dizziness, shortness of breath, fatigue, loss of memory, and insomnia are also sometimes used in its diagnosis (Leon-Velarde et al., 1997).

The prevalence of CMS varies by region and by gender. In all regions, women are protected relative to men (Table 4). CMS prevalence increases with age in men at 4,300 m in Cerro de Pasco, Peru (Monge et al., 1989). At the same altitude, hemoglobin changes little in women until after the age of the menopause (Leon-Velarde et al., 1993, 1997). Available data suggest that CMS prevalence is much lower among Tibetan compared with Han or Peruvian residents of the same altitude (Table 4). The same hemoglobin or hematocrit criteria for defining CMS were used in the Tibetan and Han studies, whereas the Peru studies used a gender-specific criteria. However, since the cutoff values used in Peru were in the same range as those employed in the Tibetan and Han studies, it is likely that the Tibetan prevalence is lower and Han prevalence not distinguishably different than in Peru. In Tibet, prevalence was higher in Han migrants than Tibetan lifelong residents at all altitudes regardless of occupation (Table 5). Almost no prevalence information is available for the Rocky Mountain region (Kryger et al., 1978c). Thus, existing data suggest that CMS prevalence is greatest in Han migrants, intermediate in lifelong Andean residents, and lowest in Tibetan highlanders.

CMS develops after years of high-altitude residence. While its cause(s) remains elusive, disordered control of breathing and/or impaired alveolar-arterial oxygen diffusion

TABLE 4. CMS prevalence (%) by region and gender¹

Altitude (m)	Males			Females		
	Peru-Han	Peru-vians	Tibetans	Peru-Han	Peru-vians	Tibetans
2,260–2,800	1.4	—	0.0	0.7	—	0.0
3,050–3,800	9.1	—	0.8	1.6	—	0.3
4,000–5,200	9.8	15.6	3.0	6.0	8.8	1.6

¹ Data are compiled by averaging existing studies for a given altitude range. A total of 29,502 adults is represented and consists of 213 males and 152 females from 4,300 m in Peru (Leon-Velarde et al., 1997; Monge et al., 1992), 12,385 male and female Tibetans and 13,233 male and female Han from 2,260–5,200 m in Qinghai Province, China (Wu et al., 1994), 1,087 male and 963 female Tibetans, and 662 male and 807 female Han from 3,050–5,200 m in the Tibet Autonomous Region, China (Xie et al., 1981).

stemming from undetected chronic obstructive lung disease are likely involved. Persons with CMS have blunted HVRs, breathe less, and have lower S_aO_2 . However, not all persons with low HVR develop CMS, and some CMS patients have hypoxic responses in the normal range (Sun et al., 1990b). Other abnormalities of ventilatory control, including a depressant effect of hypoxia on ventilation, and control of breathing during sleep are likely important (Sun et al., 1990b; Kryger et al., 1978c). Episodes of sleep-disordered breathing (see Glossary) caused arterial oxygen content to fall well below control values in CMS patients in Lhasa, whereas daytime values were similar, due to the CMS patients' higher hemoglobin concentrations (Sun et al., 1996; Kryger et al., 1978a). Oxygen delivery to the brain was further worsened during sleep-disordered breathing by a lack of cerebral vasodilator response to hypercapnia and hypoxia (Sun et al., 1996). Most persons with CMS smoke cigarettes, and a considerable proportion of the Colorado and Tibet cases had some impairment of lung function (Kryger et al., 1978b; Sun et al., 1990b). It has also been suggested that persons with CMS have an excessive bone marrow response to a given level of hypoxia, but greater serum immunoreactive erythropoietin levels have not been observed (Leon-Velarde et al., 1991).

Mortality from chronic lung disease is greater at high than low altitudes in the Rocky Mountain region and possibly among Han migrants in Tibet (Regensteiner and Moore, 1985; Kao, 1975). In Colorado, persons with emphysema or chronic bronchitis

TABLE 5. Prevalence (%) of excessive polycythemia¹ in the Tibet Autonomous Region in 3,201 male ($n = 1,749$) and female ($n = 1,452$) migrants (Han) and native highlanders (Tibetans) more than 15 years old (Xie and Pei, 1981)

Region (altitude, m)	Males			Females		
	Migrants (workers)	Natives (workers)	Natives (farmers, herders)	Migrants (workers)	Natives (workers)	Natives (farmers, herders)
Lhasa (3,658 m)	12.97	1.05	0	1.64	0	0
Gyangze (4,040 m)	31.5	4.8	1.5	3.8	0	0.3
Nagchu (4,500–4,700 m)	38.4	14.4	6.6	7.2	6.5	2.7

¹ Excessive polycythemia at 3,658 and 4,040 m was defined as red blood cell (RBC) counts $>6.5 \times 10^6/\mu\text{l}$ blood and hemoglobin (hgb) >20 g/dl blood, RBC counts $>7.15 \times 10^6/\mu\text{l}$, or hgb >22 g/dl. At 4,500–4,700 m, excessive polycythemia was considered as RBC $>7.0 \times 10^6/\mu\text{l}$ and hgb >21 g/dl, or RBC $>7.7 \times 10^6/\mu\text{l}$, or hgb >23 g/dl.

died after a shorter duration of illness and more commonly from right heart failure at high than low altitudes (Moore et al., 1982c; Renzetti et al., 1966). There are fewer elderly in Colorado due in part to increasing out-migration after age 50 as the result of complications of heart and lung disease (Regensteiner and Moore, 1985). Information about other chronic diseases in high-altitude residents is limited. The prevalence of systemic hypertension is low in Peruvian high-altitude communities (Ruiz and Penalzoa, 1977) but higher among lifelong Tibetan high-altitude residents than Han newcomers, perhaps as the result of high Tibetan salt intake (Sun, 1986).

In summary, significant mortality from CMS and other causes occurs at high altitude. Persons who die from CMS are often older-aged, but it affects persons in the early years of adulthood as well. Susceptibility to CMS appears greater among migrants than natives. Lower prevalence in Tibetan than Andean high-altitude residents suggests that generational factors and/or the degree of genetic admixture may be involved. The protection afforded Tibetans may be due in part to their higher ventilation and hypoxic ventilatory drives. More consistent, age-specific diagnostic criteria for CMS and information about the prevalence of CMS in the Rocky Mountain region are needed.

SUMMARY AND CONCLUSIONS

We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.
Through the unknown, remembered gate
When the last of earth left to discover
Is that which was the beginning....
T.S. Eliot, *Four Quartets*: "Little Gidding"

Recent studies using an expanded range of techniques have revealed differences between lifelong high-altitude residents and acclimatized newcomers as well as among resident high-altitude populations. These differences are of physiological and anthropological importance insofar as they imply that generational factors influence adaptive processes. Here we try to summarize what has been learned, indicating some of the complexity influencing the interpretation of such studies and suggesting the future studies which might be undertaken to resolve at least some of the issues remaining.

Geographical and historical circumstances differ among high-altitude populations. The Tibetan plateau is larger and more geographically remote and has been occupied by humans for a longer period of time than the Andean altiplano or Rocky Mountain plateaus. Given these distinctions, the Tibetan population is likely to have been the resident longest at high altitude. Compared with Andeans, the Tibetan gene pool is less likely to have been constricted by small numbers of initial migrants and/or severe population decline. Tibetans may also have been subject to less genetic admixture with lowland groups, although this may be changing today with the influx of large numbers of Han migrants. Admixture with lowlanders is not an issue for Rocky Mountain inhabitants, as they are persons of low-altitude ancestry. While viewed by some investigators as a limitation, the fact that Rocky Mountain residents are of low-altitude ancestry has the advantage of providing a control group with which other high-altitude populations can be compared.

Future studies are required to better document the population history, extent of genetic admixture, and relationship of genetic to physiological traits in high-altitude populations. Mitochondrial DNA (mtDNA) and y-chromosomal nuclear DNA (yDNA) offer special advantages since they do not undergo recombination. In addition, mtDNA appears to accumulate mutations more rapidly than nuclear DNA (nDNA) (Giles et al., 1980). However, since gene flow is usually sex-specific, admixture estimates vary depending on what kind of DNA is employed. For example, in the San Luis Valley of Colorado, intermarriage between Native Americans and Spanish-Americans is disproportionately between Native American women and Hispanic men. As a result, 87% of Hispanic persons had mtDNA of Native American origin, whereas in the same individuals the estimate of Native American admixture using nDNA was 48% (Merriwether et al., 1995). In an analogous situation, a greater degree of European admixture was inferred in Central American tribes when yDNA rather than mtDNA was evaluated, indicating that the European contribution to Central American gene pools was predominantly male in origin (Torroni et al., 1994a). The relevance for high-altitude populations is that admixture with Europeans may not be detected in Andean populations using mtDNA alone. Correspondingly, Mongolian conquest and movements of male traders would be expected to yield higher yDNA than mtDNA admixture estimates in Tibetans. The possibility exists that such differences in admixture estimates might be useful for inferring patterns of contact although such analyses quickly become very complicated. Other cultural practices can also influence mtDNA variation; for example, polygyny would be expected to increase and female infanticide to decrease mtDNA variation.

Several differences in adaptive success between natives and newcomers have been identified. Lifelong high-altitude residents of the Andes and/or Himalayas have the following distinctions when compared with acclimatized newcomers:

- less intrauterine growth retardation;

- better neonatal oxygenation and involution of fetal cardiopulmonar characteristics;
- enlarged lung volumes and decreased alveolar-arterial oxygen diffusion gradients;
- higher maximal exercise capacity ($\text{VO}_{2\text{max}}$);
- better maintained increase in cerebral blood flow during exercise (Tibetans);
- lower hemoglobin concentrations (Tibetans);
- less susceptibility to CMS (Tibetans).

Among high-altitude native populations, several differences in adaptive success and physiological strategy have emerged. According to an evolutionary hypothesis, the greater duration and genetic isolation of the Tibetan population would be expected to result in better adaptation, as judged by the existence of attributes associated with improved chance of reproductive success. Existing data indicate that Tibetans differ in comparison with other lifelong high-altitude residents in several ways consistent with this hypothesis:

- less intrauterine growth retardation;
- greater reliance on redistribution of blood flow than elevated arterial oxygen content to increase uteroplacental oxygen delivery during pregnancy;
- higher levels of resting ventilation and hypoxic ventilatory responsiveness;
- less hypoxic vasoconstriction and lower pulmonary arterial pressure and resistance;
- lower hemoglobin concentration;
- lower prevalence of CMS.

Several of the distinctions demonstrated by Tibetans also parallel the differences between natives and newcomers, suggesting that the degree of protection or adaptive benefit relative to newcomers is enhanced for the Tibetans. However, many of these observations are based on limited information, and the requisite comparative data from other regions is not always available or collected with the same methodologies. For example, direct comparisons of cardiac output and pulmonary arterial pressure are needed in larger numbers of Tibetan and Andean high-altitude residents at similar

levels of exercise intensity. Another feature of the above lists is that characteristics which are likely to be closely related to mortality risk (e.g. IUGR, uteroplacental blood flow, susceptibility to CMS) demonstrate clearer differences between natives and newcomers or among native populations than others, such as exercise performance. This may be the result of difficulties in accurately measuring exercise performance, given the effects of training, motivation, etc., or it may indicate that differences in exercise performance are less affected by processes of natural selection at high altitudes. The higher frequency of IUGR and preeclampsia at high altitude provides a useful opportunity to generate insights into pathophysiology. Finally, the above list demonstrates that selective pressures differ between the sexes. These differences are particularly apparent during pregnancy. The lower susceptibility to CMS among women than men raises the intriguing possibility that sex differences in adaptive processes are of lifelong significance.

There are also several points of similarity among high-altitude residents. One is the seemingly equal retardation of postnatal growth among highland infants, children, and adolescents when compared with well-validated, low-altitude NCHS standards. Since it is likely that insufficient nutrition and recurrent illnesses contribute to the growth retardation, additional studies are warranted which examine their separate and combined effects. Such studies could be usefully conducted in the Rocky Mountain region, where the effects of hypoxia alone should be more readily apparent. Studies of the interactive effects of altitude, poor nutrition, and intercurrent illness are important for regional and health-policy planners. Another, related issue concerns the impact of IUGR. Information on gestational age along with birth weight is essential for comparing birth-weight-specific mortality. This in turn requires complete population enumeration or at least large and demonstrably representative samples. With the efforts to improve health and health care in many regions of the world, such information may be forthcoming. Studies in the neonatal period and infancy are required to address the conse-

quences of preterm delivery, IUGR, poor or delayed cardiopulmonary transition, and intercurrent respiratory illness for mortality and morbidity at high altitude. Since lung volumes appear universally increased in lifelong high-altitude residents, studies are warranted to determine the kinds of growth signals selectively stimulating the lungs.

These observations suggest several conclusions regarding the convergence and complexity of adaptive events. In terms of convergence, the Himalayan plateau is likely not only to have been the longest occupied and most remote, but its occupants demonstrate several physiological advantages which are consistent with their hypothesized evolutionary advantage. In addition, the Tibetans' overall pattern of adaptation appears to result in establishing the physiological and functional attributes of sea-level residents. For example, the Tibetans' characteristics of intrauterine growth, uterine artery blood flow, hemoglobin concentrations, and pulmonary arterial pressures resemble those of healthy persons at sea level. This supports the view that some of the physiological responses commonly observed at high altitude (e.g., decreased birth weight, polycythemia, diminution of ventilation, moderate elevation in pulmonary arterial pressure) are not adaptive. It also raises the presently unanswered question of what the underlying factor(s) is that has permitted Tibetans to adapt.

In terms of complexity, it is important to recall that not just the directional forces of natural selection but also the chance-driven processes of genetic drift, gene flow, and mutation are involved in evolutionary change. These processes are exemplified by the possibly small numbers of initial migrants to the Americas, severe reductions in population size at the time of sixteenth-century European conquest, and present-day gene flow in the Andean and Himalayan regions. In addition, natural selection is not a simple process. One source of complexity is that a change in adaptation may not alter fitness and that fitness, not adaptation, directs evolutionary change. Neither organisms nor environments remain static, and hence an individual's state of adaptation must be evaluated with respect to both

historic and present-day environmental conditions (Gould and Lewontin, 1979; Lewontin, 1978). Other possible explanations of seemingly adaptive traits include close linkage with traits undergoing selective pressure, random events such as genetic drift, or allometric relationships involved in growth.

Future progress is needed to identify the genes involved in governing physiological responses to hypoxia and to determine which genetic variants (alleles) contribute to differences between natives and newcomers and/or among native populations. The methods of statistical genetics will be useful for determining whether the pattern of transmission in a large group of biologically related individuals (a family set) suggests a single gene with multiple alleles, multiple genes, differential penetrance, or non-Mendelian factors (e.g., imprinting, mosaicism, and uniparental disomy) (Weiss, 1993). Statistical genetic techniques should be accompanied by linkage analysis to determine the location of the gene(s). Candidate genes should also be chosen on the basis of being plausibly related to the trait of interest. Of interest will be whether a discrete, common set of hypoxia-sensitive genes is identified or whether there are multiple genetic factors involved that vary broadly among populations.

Future progress can also be anticipated in achieving a more integrated view of high-altitude adaptation. Part of this integration will derive from an increased understanding of the ways in which levels of biological organization are articulated and influence each other. Assistance will be provided by the increasing availability of new (and often minimally invasive) techniques for evaluating cellular metabolism, energy expenditure, and body composition. Another path toward achieving integration is likely to stem from the inclusion of a broader range of subjects, including women and men, young and old, native and newcomer. The detailed physiology of adaptation and long-term acclimatization which has been worked out in men is being extended to women in ways that consider the influences of the menstrual cycle, hormone replacement, oral contraceptives, menopause, and other gender-related influences.

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